Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Budesonide

Proprietary Product Name: Budenofalk

Sponsor: Orphan Australia Pty Ltd

October 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	Major Variation (New Indications and New Dose Form)
Decision:	Approved
Date of Decision:	11 May 2012
Active ingredient(s):	Budesonide
Product Name(s):	Budenofalk
Sponsor's Name and Address:	Orphan Australia Pty Ltd, 34-36 Chandos Street, St Leonards NSW 2065
Dose form(s):	Capsules and Foam
Strength(s):	Enteric capsule 3 mg Foam enema 2 mg per actuation
Container(s):	Blister pack (capsules) Aluminium can with metering valve (enema)
Pack size(s):	Capsules: 9, 45 & 90 Enema: 1 or 2 cans per carton (each can sufficient for 14 applications)

Approved Therapeutic use:	Budenofalk budesonide 3 mg enteric capsules are indicated for induction of remission in patients with mild to moderately active Crohn's disease affecting the ileum and/or the ascending colon (see Clinical Trials section of the Product Information document). Budenofalk budesonide foam enema 2 mg is indicated in the treatment of active rectal and rectosigmoid disease in ulcerative colitis.
Route(s) of administration:	Oral (PO) and rectal
Dosage:	*Adults and the elderly:* Capsules: Acute Crohn's disease: 9 mg mane or 3 mg 3 times daily for 8 weeks. Foam Enema: 2 mg budesonide (one actuation) daily per rectum for adults. The attending physician determines the duration of use. An acute episode generally subsides after 6 to 8 weeks. Budenofalk 2 mg foam enema should not be used after this time.
ARTG Number (s)	179566 and 179575

Product background

Budesonide, a non-halogenated glucocorticoid structurally related to 16α hydroxyprednisolone, is an anti-inflammatory corticosteroid. This AusPAR describes the submission by the sponsor to register 2 dose forms of budesonide; an enteric capsule and a foam enema, each with different indications. For ease of reference, the clinical evaluation and the Delegate's Overview for each dose form are presented as two separate parts in this AusPAR.

Properties of budesonide

Corticosteroids regulate gene expression, resulting in glucocorticoid effects such as gluconeogenesis, proteolysis, lipolysis, suppression of inflammation and immune responses and mineralocorticoid effects such as sodium and water retention and potassium loss. It is well recognised that the use of oral and parenteral corticosteroids is limited by these effects, which manifest clinically as hypertension, impaired glucose tolerance/diabetes mellitus, increased susceptibility to infection and adverse bone metabolism effects (osteoporosis and osteonecrosis), amongst others. A particular problem is suppression of the hypothalamic-pituitary-adrenal (HPA) axis. The ideal modality of corticosteroid treatment for inflammatory bowel disease (IBD) is therefore to deposit a restricted quantity of a drug directly at the site of disease whilst limiting its systemic bioavailability.

Use of budesonide

Budesonide was first developed as a treatment for bronchial asthma and rhinitis and has since been introduced into the treatment of inflammatory bowel disease (IBD), formulated as an oral enteric controlled release capsule and as an enema.

There is no curative therapy available for Crohn's disease and ulcerative colitis. The aim of drug treatment is therefore is to induce remission in active disease, maintain remission and prevent relapse. The agents used in the treatment of these conditions and the route of administration for those agents are usually determined by the site and severity of the disease. Drug treatments available are aminosalicylates, immunosuppressive agents, corticosteroids and anti-TNFα agents. The sponsor noted that active distal ulcerative colitis and proctitis is mainly treated by topical administration of an active agent by suppositories, enemas or rectal foams, whereas pancolitis is treated either orally (PO) or intravenously (IV) with or without concomitant rectal administration.

Foam enema (2 mg)

Budesonide 2 mg (Budenofalk) foam enema was developed as a treatment for acute active ulcerative colitis. Active distal ulcerative colitis is mainly treated topically with suppositories or rectal liquid and foam enemas.

Many patients have problems retaining liquid enemas which have a high volume. To overcome this problem, the Budenofalk foam formulation has been developed with a high viscosity and small volume which is considered more convenient to administer, easier to retain, and better tolerated than liquid enemas. In order to provide an 'easy-to-handle' rectal formulation of budesonide, the manufacturer of Budenofalk has also produced a ready-to-use preparation, delivered from a canister that contains a unique valve system that allows for multiple dosing. This is said to be in contrast and preferable to Entocort which has to be freshly prepared immediately before use.

The sponsor proposes to register the new metered dose foam enema of budesonide for: *The treatment of active distal ulcerative colitis, proctitis and protosigmoiditis*.

There are currently no products containing budesonide approved for the treatment of ulcerative colitis (UC) in Australia. Entocort is an oral product containing budesonide and has an indication in the treatment of Crohn's disease.

UC is a chonic, relapsing, immune mediated, inflammatory disease of the colon that always affects the rectum, extends proximally to a variable extent and is characterised by a relapsing and remitting course. The aims of drug therapy in UC are to induce remission in active disease and then to maintain corticosteroid-free remission and prevent relapse. The severity of the disease and the site(s) of the affected colon determine which medicines may be used and their route of administration. In general if the disease is mild, topical (that is, rectal) therapy is often sufficient for proctitis alone, while combined topical and oral therapy is optimal for distal (left-sided) colitis. Moderate or severe, or more extensive disease requires oral or intravenous therapy.

Current treatments for active disease of the rectum/ and or distal colon include: aminosalicylates, rectal and oral corticosteroids and immunomodulatory drugs. Initial recommended therapy is a mesalazine rectal preparation with a 5-aminosalicylate oral preparation. Rectal corticosteroid therapy is added if rectal aminosalicylates have been ineffective.

It is recommended to continue rectal therapy until symptoms have resolved and then wean over several weeks. If symptoms recur, begin rectal treatment again. Rectal maintenance therapy should be considered for all patients, especially those with repeated relapses[2].

Enteric capsules (3 mg)

Budenofalk 3 mg capsules have been developed for the treatment of Crohn's disease. They contain granules of budesonide that are resistant to dissolution in gastric acid. The coating for Budenofalk starts to disintegrate at pH >6.4 and budesonide release is maximal from the terminal ileum onwards. This allows budesonide to be released locally at the site of inflammation where it can exert its anti-inflammatory effect before absorption (and first pass metabolism) can occur.

The sponsor proposes to register the new enteric-coated capsule formulation of budesonide for an indication similar to the Crohn's disease (CD) indication for current budesonide capsule formulation but with a reduced duration of treatment (8 weeks rather than 12 weeks).

Initially proposed indication**:** Treatment of mild to moderate active Crohn's disease of the ileum and/ or the colon; induction of remission in patients with active collagenous colitis.

Proposed indication: Treatment of mild to moderate active Crohn's disease of the ileum and/ or the colon.

The proposals to include a new dose group for the CD indication (that is, adolescents) and a new indication concerning active collagenous colitis have been withdrawn by the sponsor and will be further considered only with respect to safety.

Another oral capsule containing budesonide, Entocort was approved in 1996 for the induction of remission in adult patients with mild to moderate Crohn's disease affecting the ileum and/or the ascending colon with a recommended dose of 9 mg once daily in the morning. Entocort is approved for no more than 12 weeks in any single course and the indication is restricted to adults.

Crohn's disease is a chonic, relapsing, immune mediated, inflammatory bowel disease. Current therapies include: 5-aminosalicylic acid, immunosuppressive agents such as azathioprine and mercaptapurine, corticosteroids, antibiotics and anti-TNF-α agents.

The TGA has adopted CPMP/EWP/2284/99 Rev *1 Guideline on the Development of New Medicinal Products for the Treatment of Crohn's Disease.* Pertinent recommendations from that guideline include:

- Choice of comparator will depend on the indication for which the drug is being developed.
- To support a first-line indication in the treatment of active CD it is necessary to demonstrate that the drug has either the same or an improved risk/ benefit profile as the standard of care which currently in the majority of cases includes glucocorticoids.
- Clinical trials aiming at supporting a first-line indication should always include a comparison with the accepted first-line treatment. Unless the study is aiming at demonstrating superiority, the trial should, while ethically justifiable, also include a placebo arm to provide internal validity.

Regulatory status

Budenofalk foam enema has marketing authorisations in 17 European countries and was first approved in 2006. The indication in European countries is limited to UC of the rectum and sigmoid colon in adults.

Budenofalk capsules have marketing authorisations in multiple European countries with no centralised approval. The indication for CD in the United Kingdom (UK) and Sweden is

Induction of remission in patients with mild to moderate active Crohn's disease affecting the ileum and/or ascending colon.

There are differences in the duration of treatment within European Union (EU) countries as discussed in the clinical evaluation report (CER) below (under *Clinical Findings*).

Budesonide ("Entocort") 3 mg modified release capsules are currently registered in Australia by AstraZeneca Pty Ltd for the induction of remission in adult patients with mild to moderate Crohn's disease affecting the ileum and/or the ascending colon.

Budesonide is also registered as a powder for inhalation, a nebulising solution and a nasal spray for various indications including bronchial asthma.

Product Information

The approved Product Information (PI) documents current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Budesonide is a well known drug substance that is the subject of a monograph in the European Pharmacopoeia. The drug substance proposed for use in the Budenofalk products has been assessed by the European Directorate for the Quality of Medicines (EDQM). The drug substance is practically insoluble in water and is micronised for use in the Budenofalk products.

Drug product

Foam Enema

The foam enema is an emulsion in an aluminium canister. The canister is pressurised with the propellants, propane, butane and isobutane. A metered valve releases 2 mg of budesonide per actuation. Plastic (PVC) applicators are included with the product. Each can is intended to deliver 14 × 2 mg doses and contains a 20 mg overage of budesonide (48 mg in total).

The specifications applied to the foam enema are appropriate and a shelf life of 2 years below 25°C has been established.

Enteric Capsules

The capsules contain spherical, enteric-coated beads. The finished product specifications include an appropriate dissolution test. A shelf life of 3 years with storage below 25°C has been established.

Biopharmaceutics

Budesonide is intended to act locally in the ileum and colon.

After oral administration, the systemic availability of budesonide is about 9-15%. It is about 50% higher after rectal administration. Administration of the enteric capsules with food resulted in delayed absorption but did not significantly affect the Area Under the Concentration time curve (AUC) or peak plasma concentration (C_{max}). There was no systemic accumulation of budesonide upon multiple dosing of the foam enema.

Quality summary and conclusions

There were no objections in respect of Chemistry, Manufacturing and Controls to registration of Budenofalk enteric capsules and foam enema.

III. Nonclinical findings

Introduction

In Australia, Entocort® 3 mg is currently the only budesonide oral capsule available and the maximum recommended human dose (MHRD) is 9 mg/day.

Pharmacology

Studies in which colitis was induced by intra colonic or intra rectal application of acetic acid or 2,4,6-trinitrobenzene sulfonic acid (TNBS) have shown that local administration of budesonide (intra rectal or direct into the colon) dose dependently prevents the induction of colitis, reduces diarrhoea and reduces pathological damage in the colon.[1, 2, 3, 4, 5, 6, 7] No experimental studies investigating potential pharmacodynamic drug interactions with budesonide were conducted by the sponsor. This was acceptable as specific pharmacodynamic interactions of budesonide with other compounds are not expected to vary due to the change in formulation and/or increase in MRHD.

Pharmacokinetics

The pharmacokinetics of budesonide has been extensively documented in previous submissions to the TGA of budesonide containing products (Entocort®, Pulmicort®, Budamax®). No new animal pharmacokinetic studies were submitted with the present Budenofalk® application.

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[1] Fabia R, Ar'Rajab A, Willén R, Brattsand R, Erlansson M, Svensjö E. The effect of locally or systemically administered budesonide on acetic acid induced acute colitis in the rat. In Fabia R, PhD thesis. Ulcerative and experimental colitis: pathophysiology as basis for therapeutic intervention. Lund University, Sweden;1993. p. II1-II9.

[2] Fabia R, Ar'Rajab A, Willén R, Brattsand R, Erlansson M, Svensjö E. Topical anticolitic efficacy and selectivity of the glucocorticoid budesonide in a new model of acetic acid-induced acute colitis in the rat. Aliment Pharmacol Ther 1994; 8:433-446.

[3] Van Rees EP, Soesatyo M, Palmen MHJH, Peña AS, Meuwissen SGM. The American gastroenterological association and digestive disease week. Gastroenterology 1993; 4(Suppl 104):A795.

[4] Palmen MJHJ, Dieleman LA, Soesatyo MA, Peña S, Meuwissen SGM, van Rees EP. Effects of local budesonide treatment on the cell-mediated immune response in acute and relapsing colitis in rats. Dig Dis Sci 1998; 43(11):2518-25.

[5] Martinsson T, Ljung T, Rubio C, Hellstrom PM. Beneficial effects of ropivacaine in rat experimental colitis. J Pharmacol Exp Ther 1999; 291: 642-7.

[6] Jacobson K, McHugh K, Svensjo E, Brattsand R, Collins SM. Budesonide enemas prevent extensive changes in the enteric nervous system in rats with experimental colitis. Gastroenterology 1993; 4(104):A718.

[7] Sanovic S, Lamb DP, Blennerhasset MG. Damage to the enteric nervous system in experimental colitis. Am J Pathol 1999; 155(4):1051-7.

The systemic availability of budesonide from Budenofalk® Capsules in patients was approximately 9-13% (proposed PI). Entocort® capsules, which have similar release properties compared to Budenofalk® capsules also displays a low systemic bioavailability of 9-12%[8]. The low systemic availability of budesonide after oral administration is mainly due to strong first-pass metabolism.[9] However, at least in man part of the absorbed budesonide is already metabolised in the gut wall.[10, 11] This pre systemic metabolism further contributes to low systemic availability of orally administered budesonide. High first pass metabolism (about 90%) limits systemic exposure from the ingested portion of the dose. Budesonide is highly protein-bound in plasma, with approximately 90% of budesonide bound to plasma proteins in humans, rats, and dogs.[12]

Toxicology

Repeat dose toxicity and local tolerance

In dogs, rectal administration of Budenofalk® Foam over 2 or 4 weeks at a dose of 1.51-1.67 mg/animal twice daily (230-300 µg/kg/day, approximately 6-7.5 fold above the MRHD of 40 µg/kg/day) did not result in any signs of systemic toxicity, probably due to the limited systemic availability after rectal administration and intestinal uptake. No kinetic data are available for rectal administration in animals so a direct comparison of exposure between animals and humans is not possible. In man, rectal administration of Budenofalk® Foam leads to a systemic bioavailability of 13.8-15.3% (proposed PI), which is slightly higher than the systemic availability after oral administration of Budenofalk® Capsules (9-13%; proposed PI). However, as the budesonide dose at the MRHD of Budenofalk® Foam is only approximately 20% of that at the MRHD for Budenofalk® Capsules, the resulting systemic exposure with budesonide under therapeutic conditions at MRHD level is lower with Budenofalk® Foam than with Budenofalk® Capsules. In these repeat dose dog studies there was no evidence of local intolerance from the twice daily rectal doses of budesonide.

Systemic Toxicity

The maximum proposed dose of Budenofalk® Capsules (12 mg/day for the first 4 weeks in adolescents) is 33% higher than the currently approved MRHD for the registered Entocort® (9 mg/day) capsules. Thus, systemic exposure after the maximum dose of Budenofalk® capsules could potentially be higher than that resulting from the maximum Entocort® dose, resulting in an increased potential for systemic toxicity. Furthermore, Budenofalk® Capsules are proposed for use in adolescents at doses up to 12 mg/day, whereas Entocort® is only indicated for adults.

[8] Edsbäcker S, Andersson T. Pharmacokinetics of budesonide (Entocort™ EC) capsules for Crohn's disease. Clin Pharmacokinet 2004;43:803-821.

[9] Ryrfeldt A, Squire RA, Ekman L. Liver tumors in male rats following treatment with glucocorticosteroids. Toxicol Pathol 1992; 20(1):115-117.

[10] Dilger K, Schwab M, Fromm MF. Identification of budesonide and prednisone as substrates of the intestinal drug efflux pump P-glycoprotein. Inflamm Bowel Dis 2004; 10(5):578-83.

[11] Maier A, Zimmermann C, Beglinger C, Drewe J, Gutmann H. Effects of budesonide on P-glycoprotein expression in intestinal cell lines. Br J Pharmacol 2007; 150:361-8.

[12] Andersson P, Appelgren LE, Ryrfeldt A. Tissue distribution and fate of budesonide in the mouse. Acta pharmacol et toxicol 1986; 59:392-402

The clinical exposure to budesonide at the MRHD of Budenofalk® Capsules was compared with known exposure at the MRHD of Entocort® capsules, as previously accepted safety margins may have required re-assessment. It was noted that the sponsor did not use the maximal dose of 12 mg/day in the supporting Clinical studies (9 mg/day was used).

Table 1a. Relative exposure

Study details	Species	Dose (mg/day)	$AUC_{0\text{-}24h}$	$AUC_{0\text{-}24h}$ (ng.h/mL)*	Relative exposure †
Edsbacker (2004)	Human volunteers (n=24)	9 mg Entocort® capsules single dose	5.7 µg*h/L	5.7	0.42
BUC-59/BIO (Budenofalk 3 mg tablets); single dose Clinical study (from proposed PI)	Human volunteers (n=18); PO	9 mg in the morning	10.2 ng.h/mL ($AUC_{0\text{-}inf}$)	10.2	NA
12 mg (extrapolated from 9 mg)	Human volunteers (n=18); PO	9 mg in the morning	13.6	13.6	1
Budenofalk® foam (2 mg for 5 days) (from proposed PI)	Human volunteers (n=18); rectal	2 mg	5.4 (day 1) 4.3 (day 5) ng.h/mL	5.4 4.3	NA NA

† = calculated as animal:human AUC_{0-24h} using 13.6 ng.h/mL as the estimated human AUC based on the recommended clinical dose of 12 mg/day (extrapolated from 9 mg/day data); * = all values converted to ng.h/mL; nd, no data; NA, not applicable.

Table 1b. Human exposure

Study details	Species	Dose (mg/kg/day)	Plasma AUC0-inf	
			16-α-hydroxy-prednisolone ne	**6-â-hydroxy-budesonide**
BUC-59/BIO (Budenofalk® 3 mg tablets)	Human volunteers (n=18)	9 mg in the morning	119.2 h*ng/mL	25.5 h*ng/mL

Therefore, the use of the Budenofalk® products at their proposed MRHDs is unlikely to elicit any additional systemic toxicities.

Budenofalk® Foam impurity

Drug substance impurity levels of all Budenofalk® preparations are reported to comply with the relevant European Pharmacopeia monograph (sponsor's Quality Overall Summary). Therefore, nonclinical safety studies for toxicological qualification of active pharmaceutical ingredients (API) impurities were not deemed necessary.

For a product with a maximal daily dose of <10 mg, the impurity qualification theshold is 1% or 50 µg total daily intake (whichever is lower)[13]. As the maximal daily dose of Budenofalk® Foam is 2 mg, the qualification theshold is 1%. As the proposed shelf-life specification limit for the degradation product is ≤0.8%, toxicological qualification is not necessary. Toxicological studies on the main degradation product were nevertheless conducted:

- Single dose IV study in NMRI mice.
- Mutagenicity study in the Ames test.
- Four week repeat dose study with rectal administration to beagle dogs (comparison of old batch with new batch).

In a single dose study in mice, the main degradant demonstrated a slightly higher acute toxicity after intravenous (IV) administration compared to budesonide. The systemic exposure of a patient (50 kg body weight) after treatment with Budenofalk® Foam at the MRHD (2 mg budesonide/day) containing the degradation product at the shelf-life limit (0.8%) would be approximately 0.32 µg/kg, which is approximately 100,000 fold below the No Observable Effect Level (NOEL). A dose comparison between the NOEL in an acute IV rodent study and the potential clinical 'dose' of an impurity in a rectal foam is not very meaningful for risk assessment purposes, apart from documenting the relatively non toxic nature of the degradant. An Ames test did not reveal evidence for a genotoxic potential the main degradant. Furthermore, a 4 week rectal local tolerance study in showed no difference between an old (degraded) Budenofalk® Foam batch containing the degradant at a level (1.02%) exceeding the shelf-life limit and a new Budenofalk® Foam batch (containing little/no degradation products) or placebo foam.

In conclusion, the degradation product of budesonide does not require toxicological qualification at the proposed specification limits and limited toxicological data did not suggest any untoward toxicological properties. Thus, it was considered that the degradation product at the proposed specification will not affect the safety profile of Budenofalk® Foam.

Genotoxicity

Budesonide is not considered to possess genotoxic potential based on published studies with bacterial gene mutation assays and a mouse micronucleus test (assessed in this report), consistent with previous assessments for this compound (published PI documents for Entocort®, Pulmicort®, Budamax®).

As discussed above under Budenofalk® Foam impurity, the degradant was negative in a bacterial gene mutation assay (Ames test).

[13] Q3B(R2): *Note for Guidance on Impurities in New Drug Products*, CPMP/ICH/2738/99; June 2006.

Carcinogenicity

The sponsor submitted four rodent carcinogenicity studies which are available in the public domain (one published, thee in a product monograph for Entocort® capsules). These studies have been evaluated by the TGA during the evaluation of previous submissions and appropriate statements appear in the PI document for Entocort® and other registered budesonide containing products. The new data provided in the current submission for Budenofalk® does not alter the previously assessed carcinogenicity profile.

Reproductive toxicity

Reproductive studies submitted were all performed using the subcutaneous (SC) route of administration. The studies included a fertility study and a peri/postnatal study in rats (at 0.8, 4, 20 µg/kg/day), a teratology study in rats (at 0, 4, 20, 100 µg/kg/day), and a teratology study in rabbits (at 5, 25, 125 µg/kg/day). Based on signs of parental toxicity such as effects on body weight and systemic glucocorticoid effects, dose levels appeared to have been adequate. In rats, there were no adverse effects on reproductive parameters at doses up to 4 µg/kg/day; higher doses were associated with maternal and embryofetal toxicity, although no teratogenicity was found with dosing during organogenesis up to 100 µg/kg/day and no effects on fertility at doses up to 20 µg/kg/day were noted. In rabbits, teratogenicity was seen at SC doses of 25 µg/kg/day (brachygnathia superior with fusion of frontal and nasal bones and visceral abnormalities) with a theshold dose of 5 µg/kg/day (visceral abnormalities only), concomitant with signs of maternal and embryofetal toxicity (reductions in doe body weight gain/body weight and litter/fetal weights, reduced ossification). No toxicokinetic data are available to compare with clinical exposures.

The nonclinical reproductive toxicity of budesonide has also been assessed in previous submissions to the TGA for registration of budesonide containing products (PI documents for Entocort®, Pulmicort® and Budamax®). The new data provided in the current submission for Budenofalk® were consistent with the previously assessed reproductive toxicity profile.

Nonclinical summary and conclusions

- The nonclinical dataset includes sponsor study reports and published studies. New nonclinical data include IV toxicity studies using budesonide and an impurity, 2-4 week repeat dose toxicity studies using rectal administration, a mutagenicity study and other published studies.
- The foam contains 5 new degradants; the main one was assessed in toxicological studies. It was negative in a bacterial gene mutation assay and slightly more toxic by acute IV administration in mice. There were no differences observed following 4 weeks rectal administration of budesonide foam with and without the main degradant (1%) in dogs. In any event, the proposed specification for this impurity in the foam enema does not require toxicological qualification.[14]
- The clinical systemic exposures (plasma AUC) to budesonide at the maximal doses of Budenofalk® Capsules (9 and 12 mg/day) and Budenofalk® Foam Enema (2 mg/day) were less than budesonide exposure from the MRHD of Entocort® capsules (9 mg/day).
- In dogs, rectal administration of Budenofalk® Foam over 2 or 4 weeks at a dose of 3.0-3.3 mg/day (230-300 µg/kg/day, approximately 6-7.5 times the maximal

[14] CPMP/ICH/2738/99. Impurities in New Drug Products. Note For Guidance On Impurities in New Drug Products. http://www.tga.gov.au/pdf/euguide/ich273899enrev2.pdf

recommended human dose of 40 µg/kg/day) did not result in any signs of systemic toxicity or local intolerance.

- Rodent carcinogenicity studies conducted for Entocort® were submitted. No increase in tumours was observed in mice at budesonide dose levels of up to 200 µg/kg/day in drinking water. An increase in malignant gliomas was observed in male Sprague-Dawley (SD) rats dosed at 50 µg/kg/day in drinking water was seen in the first rat carcinogenicity study but this was not reproduced in two subsequent studies in SD and Fischer 344 rats. An increased incidence of hepatocellular tumours was observed in both male SD rat studies (no hepatic data for F344 rats), an effect also demonstrated for two other glucocorticoids (prednisolone and triamcinolone acetonide).
- Published SC reproductive toxicity studies showed embryofetal toxicity at doses of ³ 20 µg/kg/day in rats (NOEL 4 µg/kg/day) and ³ 5 µg/kg/day in rabbits (no NOEL determined), concomitant with maternal toxicity. Teratogenic effects were seen in rabbits at 5 and 25 µg/kg/day (no NOEL determined).

Conclusions and Recommendation

There is extensive clinical experience with budesonide though the use of various budesonide containing products and its clinical efficacy and safety profiles are well established. Of particular relevance to the current submission are the registered Entocort® capsules (containing gastric acid resistant, prolonged release granules for oral use) for induction of remission in adults with mild to moderate Crohn's disease affecting the ileum and/or the ascending colon.

At the MRHD of Budenofalk® capsules (9-12 mg/day) and foam enema (2 mg/day), the clinical systemic exposure to budesonide does not exceed that resulting from the MRHD of Entocort® capsules; hence the use of the Budenofalk® products is unlikely to be associated with increased systemic glucocorticoid toxicity relative to Entocort®. Confirmatory clinical data should be assessed by the clinical evaluator.

Although no evidence of local intolerance was reported following daily rectal administration of budesonide foam to dogs for up to 4 weeks, human rectal tolerance should be confirmed by the clinical evaluator.

There are no objections on nonclinical grounds to the registration of Budenofalk® capsules and foam enema for the proposed indications.

Amendments to the draft Product Information documents were also recommended.

IV. Clinical findings

Foam Enema

Introduction

The sponsor has included company sponsored study data that compares (through a non-inferiority design) Budenofalk and Entocort enemas as pivotal data for the application.

The component of the submission for Budenofalk enteric capsules was a hybrid, containing study reports and published papers.

Budenofalk foam enema was developed as a line extension to the marketed Budenofalk oral capsule in Europe and so, unsurprisingly, the two clinical overview documents have aspects of the clinical rationale in common. Consequently, the clinical rationale presented

below includes some information that has been reproduced from the CER for Budenofalk Oral Capsules. This has been done in order to provide a complete context to the development of the Budenofalk product line.

The clinical rationale for the development of the budesonide foam enema was well presented. The information presented within the sponsor's Overview document was generally in alignment with accepted clinical practice in Australia for the diagnosis and management of mild to moderate distal ulcerative colitis.

The Therapeutic Guidelines: Gastrointestinal 2006 Version 4[15] state there is good evidence that rectal aminosalicylates are more effective than rectal corticosteroids for left-sided ulcerative colitis. Recommended initial therapy is combination rectal and oral aminosalicylates, with rectal corticosteroids (hydrocortisone acetate 10% foam or prednisone suppository 5 mg or prednisolone sodium phosphate 20 mg in 100 mL) added if these are ineffective. If the distal disease is unresponsive to this treatment, second line therapy involves the addition of an oral corticosteroid. It was recognised that the treatment chosen generally depends on the extent of disease, patient preference and tolerability of the formulation; for example liquid enemas can reach as far as the splenic flexure, while foam preparations are often better tolerated but only reach as far as the sigmoid colon.

Formulation development

Budenofalk foam enema is formulated as an emulsion plus propellant. The sponsor noted that the physical properties of any foam based on an alcoholic/aqueous system are a function of the type of dispersion, the type of glycol, the type and quantity of propellant, the surface active agents and other additives being present. Consequently, a number of formulations containing various basic dispersion phases, suitable surfactants and propellants were tested to find one that would provide the optimum expansion of foam from a compressed, pressurised state to deliver an intended dosage of 2 mg in an appropriate volume, sufficient to cover the lower colon and deliver budesonide to inflamed tissue.

The formulation chosen initially for the clinical trials program yielded l mg and 2 mg budesonide in 50 mL. That formulation was associated with retention problems and was not developed further (sponsor's *Clinical Overview*). The corresponding studies (BUF-2/UCA, BUF-3/UCA) were therefore not submitted for evaluation.

The product finally developed for marketing produces a smaller volume of foam (between 20 and 30 mL per actuation). The sponsor's *Clinical Overview* stated that, with the exception of study BUF-4/BIO, which used a ^{99m}Technetium-labelled budesonide foam, the proposed commercial formulation was used in all phases of clinical trials.

Evaluator's comment

The following points were noted in the sponsor's submission:

- sorbic acid was used as an antimicrobial preservative thoughout the pharmaceutical and clinical development program. It was removed from the formulation and replaced by propylene glycol post-approval in Europe as a result of the assessment of an application by the German Federal Institute for Drugs and Medical Devices (BfArM-Bundesamt für Arzneimittel und Medizinprodukte).
- This is of concern because locally applied, locally acting products cannot be considered essentially similar. Even small differences in the composition (including non active

[15] Therapeutic Guidelines Ltd (2009). *Therapeutic Guidelines: Gastrointestinal 2006 Version 4.* Melbourne, Therapeutic Guidelines Ltd.

substances) of such products may influence their physicochemical properties, such as the stiffness and stability of the foam, which may affect the extent of penetration of the active compound. Consequently, therapeutic equivalence has to be shown (as per the relevant guideline[16]). There were no data assessing the impact of the formulation change or any justification as to why an assessment was not necessary.

- The batch used in Study BUF-5/UCA, a Phase IIb dose finding study was outside the lower release specification (RS) for budesonide assay (93.3% versus the RS range 95 – 105%) and sorbic acid content (83.5% versus RS range 90 – 110%).

Note: The sponsor's response to these comments is considered below (under *List Of Questions*).

Excipients

The proposed formulation contains the excipients cetyl alcohol, emulsifying wax, purified water, disodium edetate, macrogol stearyl ether, propylene glycol and citric acid monohydrate, with propane, n-butane and isobutane as propellants.

The following EU Guidelines adopted by the TGA are relevant to this submission:

- Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis (CHMP/EWP/18463/2006); and
- Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents, pp 193 – 198 of The Rules Governing Medicinal Products in the European Union 1998 (3C) – 3CC12a.

Contents of the clinical submission

All data submitted in support of the registration of Budenofalk foam enema were generated from company sponsored studies and presented as final study reports. The submission contained the following clinical information:

Clinical data:

- 2 clinical pharmacology studies, 1 of which that provided pharmacokinetic (PK) data only (BUF-4/BIO) and 1 of which provided PK/PD data (BUF-7/BIO);
- 1 Phase IIb dose finding efficacy/safety study containing a placebo arm as well as 2 mg once a day (o.d.) and twice a day (b.d.) doses of budesonide study (BUF-5/UCA*); and
- 2 Phase III efficacy/safety studies, comprising
  - 1 comparative study with Colifoam hydrocortisone acetate (BUF-6/UCA*);
  - 1 non-inferiority study with Entocort enema (BUF-9/UCA*).
- * Studies BUF-5/UCA, BUF-6/UCA and BUF-9/UCA also examined pharmacodynamic effects of rectal budesonide such as serum cortisol levels, osteocalcin and bone-specific alkaline phosphatase

Evaluator's comment. Choice of comparators for Phase III studies

The comparators used in the Phase III efficacy and safety studies are of particular note. In Study BUF-6/UCA the comparator was Colifoam (hydrocortisone acetate). Although Colifoam 10% weight/weight (w/w) hydrocortisone acetate rectal foam cream (Aspen Pharmacare) is entered on the Australian Register of Therapeutic Goods (ARTG entry

[16]Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents, pp 193 – 198 of The Rules Governing Medicinal Products in the European Union 1998 (3C) – 3CC12a.

43026) with an indication for the topical treatment of inflammation occurring in rectal mucosa, it appears the Australian registered Colifoam product and the Colifoam product used in Study BUF-6/UCA are not one and the same. They have different manufacturers and different propellants. The difference in composition is of concern with respect to therapeutic equivalence (see earlier discussion at 2.2.1 of this evaluation report).

The sponsor has not provided any data to demonstrate the therapeutic equivalence of the study comparator with currently approved Australian product or justification as to why this is not required.

In Study BUF-9/UCA, Entocort liquid enema was used as the comparator in a non-inferiority study. This product has never been registered in Australia.

Consequently, it is unknown to the TGA if Entocort liquid enemas have an acceptable level of efficacy and safety. In this context, a non-inferiority study is fairly meaningless because what may in fact be demonstrated is that the test drug is non inferior to something that may not work. However, some level of reassurance can be taken from the fact that Entocort enemas have been approved in the UK and Sweden. In addition, the sponsor has cited several references that are purported to show that Entocort enemas have statistically and clinically significant benefits compared to placebo in terms of clinical and endoscopic remission rates. These references, which were included in the current submission for information only, assume much greater importance in the context of an Australian submission and essentially require evaluation to substantiate the efficacy of Entocort enemas. This is considered further below in this CER.

Note: The sponsor provided a detailed discussion of the choice of comparators in its response to these comments (see below *List of Questions*).

Evaluator's comment. Sponsor's choice of Study BUF-6/UCA as a pivotal study

The sponsor has stated that BUF-6/UCA and BUF-9/UCA are pivotal studies. Putting aside the issue of comparators, the clinicalevaluator was concerned that Study BUF-6/UCA was an open label study, that is, both patients and the investigator were aware of the treatment received, which introduces significant potential for bias into a study that relied heavily on subjective assessments for determination of the primary and most secondary efficacy endpoints. Furthermore, it is of note that the TGA adopted EU guideline states that Phase III studies in ulcerative colitis should, amongst other requirements, be double blinded (see also '*Other concerns*', below).

Moreover, in this equivalence study the lower bound of the 95% confidence interval for the difference in proportion of responses between budesonide foam and its comparator in the analysis of the per protocol population (PP), which was the primary population, actually lay slightly below the pre defined lower boundary of -10%, at -10.6% and well above the predefined upper boundary of +10%. That is, the study did not demonstrate equivalence according to the a priori criteria. Also, analysis of the Intent-to-Treat (ITT) population gave a 95%CI lower bound of -12.3%, and when patients with no recorded 'last observation carried forward' (LOCF) (who for the purposes of the PP and ITT analyses were classified as non-remission) were excluded from both analyses, the lower bounds from the PP and ITT population analyses were even lower at -14.5% and -15.8%, respectively.

In view of the potential for bias in Study BUF-6/UCA and the failure to convincingly demonstrate equivalence (PP and ITT analyses are equally as important for such studies), the clinicalevaluator considered this can at best be a supporting study. This study is discussed further below.

Note: In its response to the first round evaluation report the sponsor provided a detailed justification for considering BUF-6/UCA to be a pivotal study. The justification was considered further and accepted (see below under *List of Questions*).

Evaluator's comment. other concerns

The sponsor submitted an out-of-date submission. The sponsor's *Clinical Overview* for the foam enema dated from July 2004 and was written specifically for EU submission. No post marketing experience data were presented in the current submission for the foam enema, despite its international birthday having been in 2006.

The sponsor's *Clinical Overview* also stated that specific EU guidelines for clinical trials of ulcerative colitis were not available. Whilst this was true at the time of writing of the overview, a *Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis (CHMP/EWP/18463/2006)* has since been promulgated in the EU and adopted by the TGA. Consequently, the sponsor's overview does not address the extent to which the data contained within the submission satisfies the TGA's current requirements.

Note: This has been addressed in the sponsor's response to the first round evaluation questions (see below under *List of Questions*).

Good clinical practice

All clinical studies included in the application were carried out in accordance with:

- The Declaration of Helsinki concerning medical research in humans (adopted by the 18th World Medical Assembly, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, and Somerset West, South Africa 1996): and
- The EU Guidelines (CPMP) on Good Clinical Practice for trials on medicinal products in the European Community 1991and the ICH recommendations implemented January 1997.

Pharmacokinetics

A limited biopharmaceutical development program was undertaken for Budenofalk foam enemas and involved 18 healthy male Caucasian adults and 12 Caucasian patients with active ulcerative colitis (Table 2). The program was limited because the pharmacological properties of oral as well as rectal budesonide were said to have been extensively investigated already as part of the development program for the Budenofalk oral capsules and the development of AstraZeneca's Entocort budesonide enemas. Summaries of the pharmacokinetic studies are presented below.

Table 2. Submitted pharmacokinetic studies

PK topic	Subtopic	n	Study ID	*
PK in healthy adults	General PK. Single dose	18	BUF-7/BIO	*
	Multi-dose	18	BUF-7/BIO	*
PK in special populations	Target population § Single dose	12	BUF-4/BIO	
	Multi-dose		No studies	
	Colonic spread, distribution	12	BUF-4/BIO	*

PK topic	Subtopic	n	Study ID	*
	Hepatic impairment		No studies	
	Renal impairment		No studies	
	Neonates/infants/children/adolescents		No studies	
	Elderly		No studies	
Genetic/gender-related PK			No studies	
PK interactions			No studies	
Population PK analyses	Healthy subjects		No studies	
	Target population		No studies	

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration. However, a number of concerns were raised with respect to Studies BUF-7/BIO and BUF-4/BIO that required clarification, as discussed below.

Study summaries

Study BUF-7/BIO. Pharmacokinetics of rectally administered budesonide in healthy volunteers

The objectives of this prospective, uncontrolled, open label, single centre clinical Phase I study were to evaluate the pharmacokinetic profiles of single and multiple (steady state) dosing of 2 mg budesonide in 18 healthy male volunteers aged 21 to 40 years and to observe systemic pharmacodynamic effects on lymphocyte and neutrophil counts and serum cortisol levels. The systemic pharmacodynamic effects are presented below.

Male volunteers with normal medical history, physical examination, chest X-ray (CXR) and electrocardiogram (ECG), with laboratory parameters within ± 10% of normal range were eligible for inclusion in the study. Subjects with alcohol/drug abuse, current or past gastrointestinal, hepatic or renal disease or allergy to budesonide were excluded.

Subjects received a single dose of 2 mg budesonide (Budenofalk foam enema) rectally on Day 1 and twice daily doses of 2 mg budesonide (8 am and 8 pm) on Ddays 2 to 5. Full pharmacokinetic and pharmacodynamic profiles were assessed over 24 h on Days 1 and 5. Only the 8 am and 8 pm time points were assessed on Days 2-4. Samples were assayed for budesonide concentrations using validated high pressure liquid chomatography (HPLC)/mass spectroscopy (MS) with a lower limit of quantification (LLQ) of 0.1 ng/mL serum. The primary pharmacokinetic pharmacokinetic parameters were time to peak plasma concentration (t_{max}), C_{max}, AUC from time zero to infinity (AUC_0-∞), elimination rate constant (ke), mean residence time (MRT) and clearance.

The sample size was calculated *a priori*. A total of 17 subjects were required to give the study power 80%, with α =0.05, to detect a 30% difference in budesonide concentrations between the first and last dose measurement on Days 1 and 5, assuming the standard deviation of the measurements was 35% of the average first dose measurements and the correlation between the first and last dose measurements was 0.3.

Results

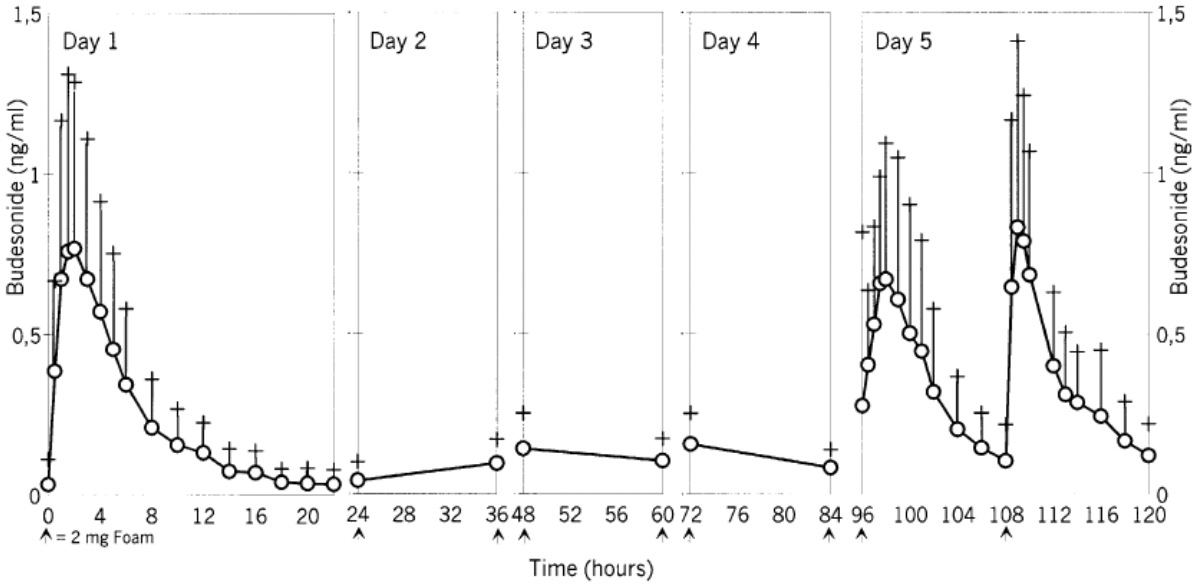
A total of 19 volunteers, all Caucasian were enrolled and 18 (mean (± standard deviation (SD)) age 25.9 ± 2.9 years (yrs) [range 20 – 31yrs]; mean (± SD) body weight 75.6 ± 6.0 kg [range 64-85 kg]; mean (± SD) height 180.4 ± 5.5 cm [range 172 - 190cm]) completed the study. One subject discontinued from the study as he was unavailable for a repeat of study session one (that is, single dose) and was subsequently replaced by another subject (as allowed by the protocol). Two subjects had to repeat the first study session one day later because an insufficient amount of foam was released from the container on Day 1 (as determined by weighing of the canisters after administration). Only one protocol deviation was reported: that being the inclusion of one subject who was only 20 years of age.

The key pharmacokinetic parameters as presented in the study report are summarised in Table 3, which has been adapted from the study report by the clinical evaluator to include the range of values and coefficient of variation for some of the key parameters. Figure 1 shows the mean budesonide concentration-time curves over the course of the study.

Table 3. Key pharmacokinetic parameters - Study BUF-7/BIO

	Day 1			**Day 5**			**p**
	Mean (± SD)	**Range**	**CV**	**Mean (± SD)**	**Range**	**CV**	**(t-test)**
n	18			18			
Dose	2.0mg			2.0mg			
k_e (h^{-1})	0.19 (± 0.07)	0.11 – 0.39					
$t_{1/2}$ (h)	4.05 (± 1.28)	1.79 – 6.40					
MRT	6.36 (± 1.73)	3.52 – 9.77					
AUC_{0-12} (ngh/ml)	4.59 (± 2.94)	0.77 – 14.4	64%	4.30 (± 2.58)	1.50 – 11.78	60%	0.299
$AUC_{0-\infty}$, AUC_{ss} (ngh/ml)	5.36 (± 3.60)	0.84 – 17.3	67%	4.30 (± 2.58)	1.50 – 11.78	60%	0.051
Cl/f (L/min)	9.33 (± 8.36)	1.93 – 39.7	90%	10.10 (± 5.14)	2.83 – 22.24	51%	0.346
t_{max} (h)	2.14 (± 1.28)	1.0 – 5.0	60%	1.81 (± 0.88)	0.75 – 4.75	41%	0.172
C_{max} (ng/ml)	0.84 (± 0.55)	0.14 – 2.46	65%	0.90 (± 0.49)	0.41 – 2.26	54%	0.313

Figure 1. Mean (± SD) serum budesonide concentrations after rectal administration - Study BUF-7/BIO



Peak concentrations of budesonide were 0.84 ± 0.55 ng/mL after single dosing versus 0.90 ± 0.49ng/mL at steady state (t-test p = 0.313), observed at 2.1 versus 1.8 h post administration, respectively (t-test p = 0.172). Absorption profiles were said to have not changed after multiple dosing based on the mean concentration time curves and the absence of any significant differences observed in t_{max} after single and multiple dosing. $AUC_{0-\infty}$ after single dosing was 5.36 ng.h/ml compared with 4.30 ng.h/ml for a single dosing interval on Day 5 (t-test p = 0.051). There was no evidence of significant accumulation of budesonide. The bioavailability of budesonide was calculated to be 15.3 % and 13.8% for single and multiple dosing, respectively.

Evaluator's comments

Considerable inter individual variation was observed in the pharmacokinetic profiles obtained following single and multiple dosing. Intra individual variability in the profiles over the two dosing intervals on Day 5 was also notable in some patients, particularly with respect to Cmax. To give an indication of the degree of the variability between the two doses on Day 5, the ratio of Cmax for dose 2: dose 1 on Day 5 (calculated by the clinical evaluator) ranged from 0.45 to 2.56 (mean ± SD 1.24 ± 0.59; median 1.11; CV 48%). tmax also varied between the two doses on Dday 5 with the dose 2: dose 1 ratio ranging from 0.25 to 5.3 (mean ± SD 0.96 ± 1.24; median 0.5; CV 129%). A similar comparison of the individual subject AUCs for each dose interval on Day 5 was not possible because these data were not presented.

In order to allow comparisons of single and multiple dosing, the sponsor compared results from Day 1 with a single set of pharmacokinetic parameters for one dosing interval at steady state, derived by averaging the Cmax and tmax values obtained over the two dosing intervals and dividing AUC between 96 and 120 h (AUC96-120) by 2. The latter was justified by the sponsor on the basis that the AUCs of the first and second dosing interval on Day 5 did not differ significantly but these data and the analysis thereof were not presented.

The importance of the above commentary is that at steady state, if clearance remains the same and is not concentration-dependent, the area under the plasma concentration-time curve during the dosing interval will be equivalent to the area under the curve from a single dose, provided the doses are the same. The question in the clinical evaluator's mind was the extent to which the doses were the same, given the method of delivery is one

which could result in deposition of variable amounts of foam and therefore active substance. In this particular study the foam canisters were weighed after every single administration of a dose in order to record the exact administered foam dose. Interestingly, every dose (other than those given to two subjects on Day 1) was recorded as 2.0 mg. To achieve such uniformity is surprising, especially given that in BUF-4/BIO (evaluated below), where a 2 mg dose was also administered rectally and the canisters were weighed, there was much more variability, with actual budesonide doses ranging from 1.7 to 3.0 mg, with a mean ± SD of 2.1 ± 0.38.

Inspection of the tabulations of serum budesonide concentrations, the concentration-time curves and pharmacokinetic parameters for individual subjects revealed the following discrepancies:

- The budesonide concentration-time curve for one subject showed a Cmax at 96 h in excess of 2.5 ng/mL, whereas the tabulated results gave a concentration of 0.37ng/mL at that time point. Also, according to the table the highest concentration achieved at any time during that dosing interval (that is, dose 1 Day 5) was 0.49 ng/mL, achieved at 97 h (that is, 1 h post dose);
- For one subject the concentration-time curve shows the highest serum concentration of budesonide during the first dosing interval on Day 5 to have been approximately 0.8 ng/mL at 97.5 h, whereas the tabulated data has a value of 1.50 ng/mL recorded at 98 h (2h post dose);
- For one subject, the concentration-time curve shows a concentration at 0 h (immediately before dosing on Day 1) of almost 0.4 ng/mL, whereas the tabulation records a value of 0 at that time point; and
- The AUCtot (based on the 0-24 h data, calculated by the trapezoidal rule, with extrapolation from the last data point to infinity) is smaller than the AUC0-12 (also calculated using the trapezoidal rule) for two subjects on Day 1.

In the table titled Table III-1: Validation results for HPLC/MS/MS, the following were noted:

- at 2 ng/mL, the coefficient of variation (CV) for run 1 should have been 6.4% (that is, 0.14/2.16) not 14.98%, bringing the average within run precision to 5.7% not 8.6%. Given the values as originally calculated within the table were already within the required limits (of <15%), this error has no material impact on the validation of the assay;
- at the 0.06 ng/mL concentration (which is somewhat less significant because this concentration had already been considered to be below the LLOQ), the CV for run 2 should have been 30% (that is, SD/mean = 0.012/0.04) not 2.7% as recorded and, consequently, the average within run precision was 20.67% not 12.4%;
- the 0.1ng/mL sample, which represents the LLOQ, the CV for run 1 was calculated as 7.6%, whereas it should have been 74% if the mean and standard deviation were actually as recorded (that is, 0.076/0.103) and not a typographical error, which is well outside the standard 15% criterion. Consequently, the average CV across runs increases from 8% to 29.8%.

A final concern is that subject 19 was recorded as having a serum budesonide concentration of 0.15ng/mL at 0 h, that is, immediately before dosing). No explanation was provided for this result other than a statement within the analytical report that "with one exception, all blank serum samples were indistinguishable from zero ng/mL (see Appendix IV presenting the Pharmacokinetic evaluation). Thus, endogenous substances do not interfere with the assay". One would expect that such a conclusion should have been

reached in the pre study validation work (which was not included in the sponsor's submission).

Note: These issues were addressed in the sponsor's response to the first round evaluation questions (see below) see below under List of Questions.

Study BUF-4/BIO: Colonic spread and single dose pharmacokinetics of budesonide foam in patients with active ulcerative colitis

The primary objective of this prospective, open, single centre clinical Phase I study was to evaluate the colonic spread of budesonide foam. The secondary objectives were to evaluate persistence of the spread and homogeneity of the distribution of the test medication; retention time of the budesonide foam; acceptance of the foam by patients; and the pharmacokinetic profile of budesonide following application of foam, including determination of $AUC_{0\text{-}8h}$, C_{max}, t_{max}, $AUC_{0\text{-}24h}$, k_e, and the half-life ($t_{1/2}$).

Patients with mildly to moderately active ulcerative colitis and inflammation in the rectum and colon and with disease activity index (DAI) ≥ 4 at baseline were eligible for study entry. Patients with Crohn's disease, history of bowel operation or cancer, toxic megacolon or concomitant medications that could have influenced the underlying disease or interacted with budesonide were excluded.

A single 2 mg dose of ^{99m}Technetium-labelled budesonide foam was administered rectally in the morning following defaecation and retained for at least 4 h by all patients. Patients lay supine during this period. Gamma scintigraphic examination was performed immediately after dosing and at 0.05, 0.5, 1, 2, 4, and 6 h to determine the extent of distribution of the foam within the colon. The gamma camera scans were analysed by two separate assessors, who both independently evaluated the radioactivity, the homogeneity, the persistence and the spread of the foam thoughout each of seven abdominal regions: transverse colon, proximal third of descending colon, middle third of descending colon, distal third of descending colon, proximal half of sigmoid colon and distal half of sigmoid colon and rectum.

Blood samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6 and 8 h after dosing and assayed for budesonide concentrations using validated HPLC/MS with a LLOQ of 0.1 ng/mL serum.

No formal statistical analysis of the data was undertaken by the sponsor and the sample size of 12 patients was noted to have been chosen for practical reasons, rather than statistical considerations. In essence the study was undertaken for exploratory purposes

Results

A total of 12 Caucasian patients (Male:Female 8:4; mean (± SD) age 41 ± 11.2 yrs [range 28-58]) and mean (± SD) DAI 7.9 ± 1.9 [range 4-10]) were enrolled and completed the study. Of these, 11 patients had left sided colitis and 1 had proctosigmoiditis.

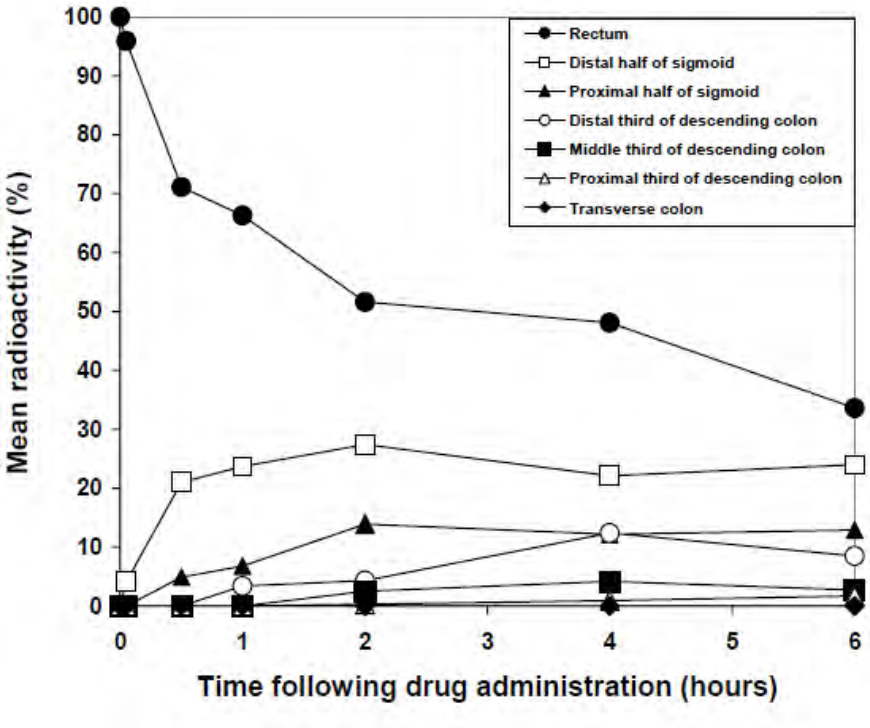
Colonic spread of budesonide

There was marked inter individual variability, with maximal spread ranging from 11 to 40 cm (mean ± SD 25.4 ± 10.3 cm), with the average time to peak spread at 4 h. Individual peaks occurred at times ranging from 0.5 to 6 h. The distal half of the sigmoid colon was reached in all patients after 2 h on average. The proximal half of the sigmoid colon was reached in 9 patients, distal third of the descending colon in 6 patients, mid third of the descending colon in 3 patients and proximal third of the descending colon in 1 patient. No radioactivity was detected in the transverse colon in any patient.

The kinetics of the spread are shown in Figure 2. On average, the radioactivity in the rectum decreased rapidly within the first 2 h and then more slowly between 2 and 6 h. Corresponding spread to the distal half of sigmoid colon was rapid (within 0.5 h), peaking at 2 h and then remaining stable over 2 to 6 h post administration, accounting for 21.0 to 27.4% of total activity. In the proximal half of the sigmoid colon, budesonide spread more

slowly but progressively to reach a maximum of 13.9% of radioactivity at 2 h. It then remained relatively stable until 4 h (12.2%) and 6 h (12.9%). The maximum level of radioactivity in the distal third of the descending colon ranged between 0-53% with a mean of 12.4% and 8.5% at 4 and 6 h, respectively.

Figure 2. Spread of budesonide foam throughout the colon – Study BUF-4/BIO



The persistence was always highest at 4 h post administration and reached highest scores in the distal half of the sigmoid colon. However, even when present, the radio labelling was not always homogenous. The study report stated that homogeneity within the distal half of the sigmoid colon was achieved in only 7/12 (58.3%) patients (Note: the clinical evaluator presumed this to be at any point in time, for the consensus rating for homogeneity at any individual time point between administration and 6 h was never greater than 4).

Pharmacokinetics

Individual and summary pharmacokinetic parameters are shown in Table 4. The mean serum budesonide concentration-time curve is shown in Figure 3. Thee individual concentration-time curves are also shown to give a sense of considerable inter individual variation in the absorption profile and systemic exposure of patients to budesonide from the rectally administered foam formulation (Figure 4). C_{max} was reached between 1.5 h and 6.0 h (median t_{max}=3.0 h) and ranged from 0.165 to 1.790 ng/mL (mean ± SD: 0.767 ± 0.456 ng/mL). AUC_{0-8} values were between 0.918 and 7.27 ng.h/mL (mean ± SD: 3.70 ± 1.89 ng.h/mL). Other parameters could be estimated in only ten patients: the mean ± SD terminal phase rate constant (k_e) was 0.232 ± 0.103 L/h and the terminal phase half-life ranged between 1.77 and 8.08 h (mean ± SD: 3.66 ± 1.83 h).

Table 4. Pharmacokinetic parameters for budesonide – Study BUF-4/BIO

Patient #	t_{max}	C_{max}	AUC(0-8h)	AUC(0-24h)	k	$t_{1/2}$
	h	ng/ml	ng.h/ml	ng.h/ml	1/h	h
1	1.5	0.383	2.38	3.39	0.180	3.84
2	4.0	1.000	5.57	7.45	0.240	2.88
3	2.0	0.754	3.92	5.96	0.139	4.99
4	6.0	0.626	2.75	.	.	.
5	4.0	1.220	6.33	7.29	0.392	1.77
6	3.0	0.165	0.918	1.84	0.086	8.08
7	2.0	1.200	4.63	5.13	0.352	1.97
8	5.0	0.428	2.07	.	.	.
9	3.0	0.567	2.68	3.05	0.317	2.18
10	1.5	1.790	7.27	9.73	0.160	4.33
11	3.0	0.499	2.85	4.38	0.155	4.47
12	2.0	0.574	3.08	3.61	0.299	2.32
Mean	3.08	0.767	3.70	5.18	0.232	3.66
SD	1.43	0.456	1.89	2.42	0.103	1.83
Max	6.00	1.790	7.27	9.73	0.392	8.08
Min	1.50	0.165	0.918	1.84	0.086	1.77
Median	3.00	0.600	2.97	4.75	0.210	3.41

Figure 3. Mean (± SD) budesonide concentration versus time – Study BUF-4/BIO

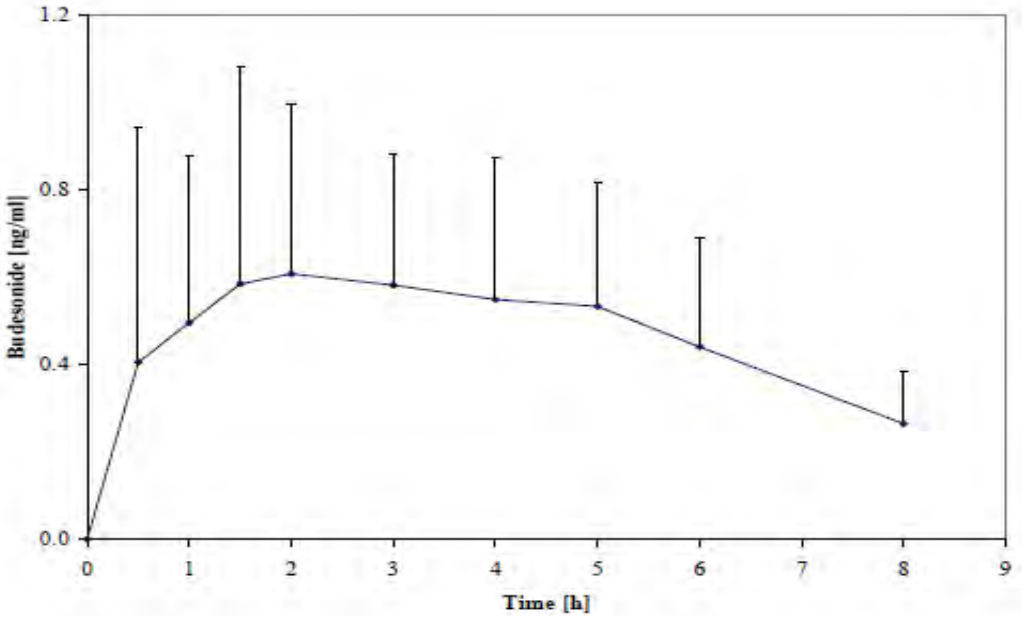
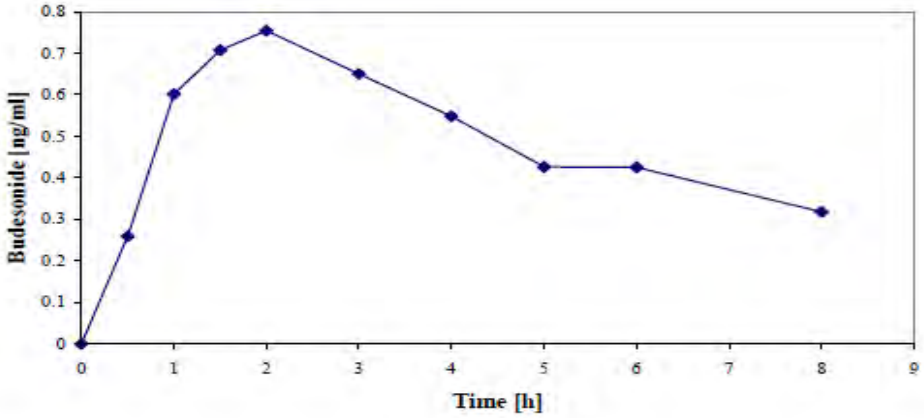
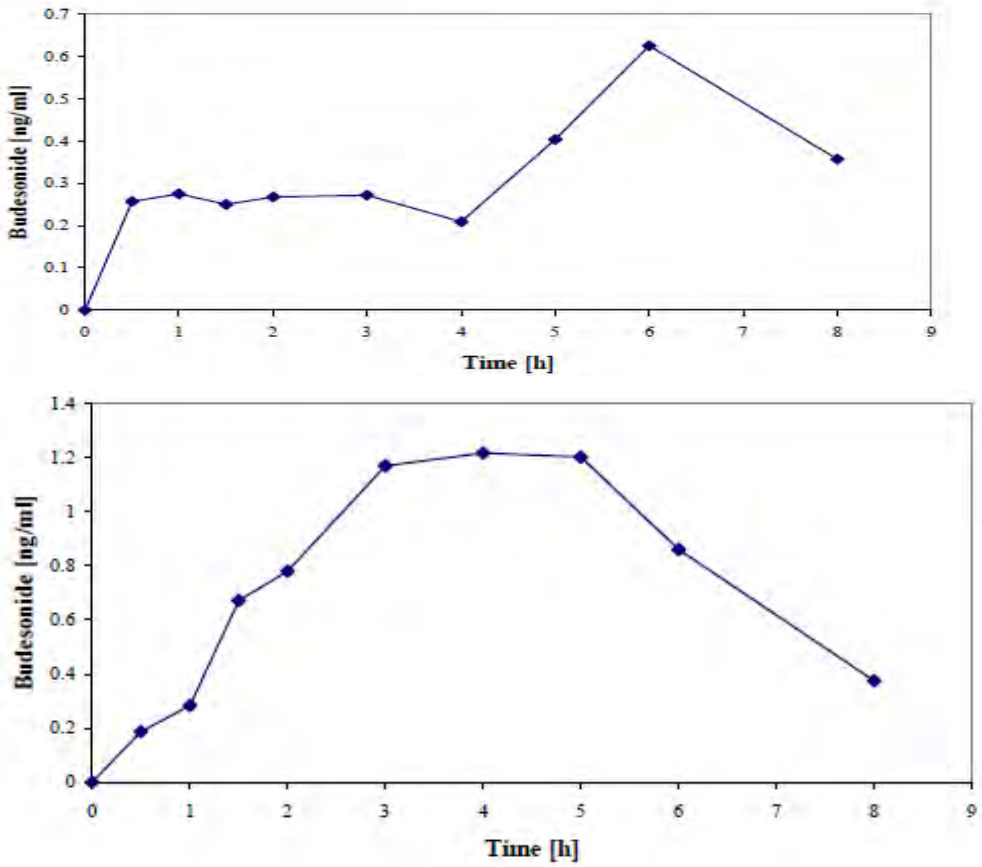


Figure 4. Serum concentration-time curves for budesonide in selected individual subjects – Study BUF-4/BIO





Evaluator's comments

This study was generally well designed from the point of view of assessing colonic spread of the foam, with several features used to maximise validity of the results:

- uniform distribution of radioactive marker within the foam was confirmed by determining the activity concentration (MBq 99mTc/g foam) of repeated actuations in a validated ionisation chamber;
- levels of radioactivity thoughout the colon were determined using standard software that included correction for attenuation differences for the different anatomical regions; and
- two separate independent assessors were used to evaluate the gamma camera scans and the in the event of a difference of opinion, a consensus analysis was performed.

However, several observations of note for the clinical evaluator were:

- there was no explicit statement about attempts to ensure that the rectum and distal colon were clear of any hard faecal matter that could have impeded the spread of the foam. This is unlikely to have been a problem though because all 12 patients had a colonoscopy performed on the day before the administration of the study drug and should have undergone bowel preparation; and
- there was a notable lack of concordance between the two assessors in their determination of homogeneity and persistence of the foam that was independent of the abdominal area analysed. The discordances (irrespective of site and time) have been summarised by the clinical evaluator in Tables 5 and 6. From Table 5 it can be appreciated there were 106 discordant assessments of homogeneity (out of a total of 504 assessments (21%)) and of these there was a discrepancy in the order of 2:1 for assessor 1 giving a lower rating than assessor 2. In contrast, as shown in Table 6, assessor 2 was more likely to give a lower rating for persistence. Out of a total of 168

scan assessments there were 48 (29%) discordances, for all of these assessor 2 considered the foam to absent while assessor 1 considered it to have varying degrees of persistence.

Table 5. Concordance* of assessments of homogeneity of radioactivity in bowel – Study BUF-4/BIO

		Assessor 2			
		Absent	**Not homogenous**	**Homogenous**	**Total**
Assessor 1	Absent	313	15	11	339
	Not homogenous	11	52	46	109
	Homogenous	1	24	31	56
	Total	325	91	88	504

* Concordance is signified by the shaded cells

Table 6. Concordance* of assessments of persistence of radioactivity in bowel – Study BUF-4/BIO

		Assessor 2				
		Absent	**Poor**	**Fair**	**Good**	**Total**
Assessor 1	Absent	120	0	0	0	120
	Poor	12	0	0	0	12
	Fair	23	0	0	0	23
	Good	13	0	0	0	13
	Total	168	0	0	0	168

* Concordance is signified by the shaded cells

Issues with the derivation of the pharmacokinetic parameters were:

- blood samples were only collected up to 8 h post dose, resulting in an insufficient number of points to be able to accurately calculate the terminal slope of the concentration time curve and, consequently terminal half life and AUC0-24. Indeed, the half life and AUC0-24 could not be estimated for 2 of the 12 patients. As a general rule the adequacy of the number of sampling time points can be judged from the requirement that the extrapolated area from the last time point to infinity accounts for no more than 10-20% of total AUC. In this particular study, in addition to those patients for whom AUC0-24 could not be estimated, the extrapolated area from the 8 h time point to 24 h was more than 20% in 6 patients and more than 10% in the remaining 4 patients (Note: the value for extrapolation beyond 24 h to infinity would have been higher again). Thus, the AUC and half life values were quite imprecise and of limited value; and
- the pharmacokinetic parameters calculated for individual patients were not corrected to compensate for differences in the dose of budesonide, which ranged from 1.7 to 3.0 mg. However, the differences in dose alone are unlikely to account for the observed inter subject variability of pharmacokinetic parameters. The clinical evaluator's own

analyses found no correlation between the dose of budesonide delivered and either Cmax or AUC, and no correlation between the extent of spread or time to maximal spread and either Cmax or AUC. Furthermore, there was no immediately apparent relationship between disease extent or severity and either the extent or speed of spread of the foam.

Protocol violations were reported for 3 patients, all of which were considered by the sponsor to have been minor. The most serious deviation was the inclusion of a patient who had received Colifoam up to 2 days prior to enrolment in the study in contravention of an exclusion criterion. The results for this patient were not suggestive of an 'outlier' and thus, the inclusion of the patient is not considered by the clinical evaluator to have invalidated the overall results of the study.

Note: These issues have been addressed in the sponsor's response to the first round evaluation questions (under List of Questions below).

Summary of Pharmacokinetics

The physicochemical characteristics and pharmacokinetics of budesonide are summarised in the CER for Budenofalk oral capsules. The information below, therefore, is limited to a summary of the spread of budesonide foam and the pharmacokinetic profile of budesonide following rectal administration.

The spread of Budenofalk foam enema

Colonic spread of Budenofalk foam enema was assessed in 12 patients with active distal ulcerative colitis. Following rectal administration, the foam enema spread to reach the distal sigmoid colon of all patients after 2 h on average and accounted for 27.4 % of the radiolabelled budesonide at 2 h. The proximal half of the sigmoid colon was reached in 9 (75%) patients, distal third of the descending colon in 6 (50%) patients, mid third of the descending colon in 3 (25%) patients and proximal third of the descending colon in 1 patient. The foam did not reach the transverse colon. The maximum spread ranged from 11 to 40 cm (mean ± SD: 25.4 ± 10.3cm), with the average time to peak at 4 h (range 0.5 to 6h).

Pharmacokinetic profile of budesonide following rectal administration in healthy subjects

Pharmacokinetic profiles were obtained from 18 healthy Caucasian male volunteers following single and multiple dosing with Budenofalk foam enema.

Single dose profile

There was considerable inter individual variation in the pharmacokinetic profiles observed following a single 2 mg rectal budesonide dose. Peak concentrations of budesonide ranged from 0.14 to 2.56 ng/mL (mean ± SD: 0.84 ± 0.55 ng/mL). The time to peak concentration ranged from 1.0 to 5.0 h (mean ± SD: 2.1 ± 1.28 h).

Systemic exposure to budesonide (as measured by AUC_{tot}) ranged from 0.84 to 17.27 ng.h/mL (mean ± SD: 5.36 ± 3.60 ng.h/mL). The systemic bioavailability of budesonide following rectal administration was calculated to be 15.3 % using clearance estimates not adjusted for oral bioavailability (Cl/f) compared to literature values obtained after intravenous administration of budesonide[17].

[17] Ryrfeldt A, Andersson P, Edsbäcker S, et al. Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. *Eur J Respir Dis* 1982; 122(Suppl): 86-95.

Multiple dose profile

A single set of pharmacokinetic parameters for one dosing interval at steady state was derived by averaging the C_{max} and t_{max} values obtained over the two dosing intervals on Day 5 of dosing and dividing the AUC for day 5 by 2. High inter individual variability was seen, with peak concentrations of budesonide ranging from 0.41 to 2.26 ng/mL (mean ± SD: 0.90 ± 0.49 ng/mL). The time to peak concentration ranged from 0.75 to 4.75 h (mean ± SD: 2.1 ± 1.28 h).

The differences in C_{max} and t_{max} after single and multiple dosing were not statistically significant.

There was no evidence of significant potential for accumulation of budesonide; the difference between AUC after a single dose and AUC_{ss} was not statistically significant and trough levels thoughout multiple dosing did not increase and remained just above the LLOQ for the assay.

Systemic bioavailability of budesonide was 13.8% with multiple dosing.

Intra individual variability in the profiles over the two dosing intervals on Day 5 was notable in some patients, particularly with respect to C_{max}. The ratio of C_{max} for dose 2: dose 1 on Day 5 ranged from 0.45 to 2.56 (mean ± SD 1.24 ± 0.59; median 1.11; CV 48%). t_{max} also varied between the two doses on Day 5 with the dose 2: dose 1 ratio ranging from 0.25 to 5.3 (mean ± SD 0.96 ± 1.24; median 0.5; CV 129%).

Pharmacokinetic profile of budesonide following rectal administration in the target population

The pharmacokinetic profile of budesonide was obtained in12 patients with active distal ulcerative colitis following a single rectal administration of Budenofalk foam enema delivering 2 mg budesonide.

Considerable inter patient variation was observed in the absorption and pharmacokinetic profile of budesonide. C_{max} was reached between 1.5 h and 6.0 h (median t_{max}=3.0 h) and ranged from 0.165 to 1.790 ng/mL (mean ± SD: 0.767 ± 0.456 ng/mL). AUC_{0-8} values were between 0.918 and 7.27 ng.h/mL (mean ± SD: 3.70 ± 1.89 ng.h/mL). Other parameters could be estimated in only 10 patients: the mean ± SD terminal phase rate constant (k_e) was 0.232 ± 0.103 L/h and the terminal phase half-life ranged between 1.77 and 8.08 h (mean ± SD: 3.66 ± 1.83 h).

Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetic data were quite limited and obtained exclusively from a Caucasian population, of whom 18 were healthy volunteers (BUF-7/BIO) and 12 were patients with active mild to moderate distal ulcerative colitis (BUF-4/BIO).

Absorption of budesonide after rectal administration is reasonably rapid and appears complete after approximately 3 h. Systemic levels are higher than with oral administration presumably because of the potential for bypass of first pass metabolism via absorption though the rectal plexus.

A number of concerns have been raised over discrepancies and apparent miscalculations in the study report for BUF-7/BIO which was conducted in healthy volunteers.

Note: The discrepancies and miscalculations identified in BUF-7/BIO have been addressed by the sponsor in its response to TGA questions (under *List of Questions*).

Pharmacodynamics

Studies providing pharmacodynamic data

No human data were presented concerning the primary pharmacodynamic effect of budesonide which, for the purpose of this submission, is considered to be its anti-inflammatory activity in the intestinal wall.

Four studies investigated pharmacodynamic effects of systemic exposure to budesonide when administered rectally (Table 7). Summaries of the pharmacodynamic aspects of these studies are presented below.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration; however, see additional comments about Studies BUF-5 and -6/UCA below.

Table 7. Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	n	*
Primary Pharmacology	Effect on inflammatory mediators in bowel mucosa	No studies		
Systemic Pharmacology	Effect on HPA axis	BUF-7/BIO	18	
		BUF-5/UCA	223	
		BUF-6/UCA	251	
		BUF-9/UCA	541	
	Effect on bone metabolism	BUF-6/UCA	251	
	Effect on blood lymphocyte and granulocyte counts	BUF-7/BIO	18	
	Effect on C-Reactive Protein (CRP)	BUF-7/BIO	18	
Gender and Age-Related Differences in PD Response	Effect of gender	No studies		
	Effect of age	No studies		
PD Interactions		No studies		
Population PD and PK-PD analyses	Healthy subjects	No studies		
	Target population	No studies		

* Indicates the primary aim of the study.

Study summaries

Study BUF-7/BIO. Systemic pharmacodynamics of rectally administered budesonide (single and multiple dosing) in healthy volunteers

The design and conduct of this study has been summarised and critiqued above.

Full 24 h pharmacodynamic profiles for serum cortisol levels and blood lymphocyte and granulocyte counts were established following a single 2 mg rectal dose of budesonide (Day 1) and multiple dosing of 2 mg b.d. (Day 5). Cumulative 24 h serum cortisol levels and cumulative effects on granulocyte and lymphocyte counts (expressed as changes in the area under the granulocyte or lymphocyte time curve for the 24 h observation period) were determined on Days 1 and 5. On Days 2 to 4, parameters were measured at 8 am and 8 pm only.

Effect on serum cortisol

The time courses of mean serum cortisol levels after a single (Day 1) and multiple (Day 5) rectal dosing of budesonide are shown in Figure 5.

By Day 5 mean serum cortisol levels were generally lower than at the same time points on Day 1. This is reflected in the cumulative 24 h serum cortisol levels on Day 5 after multiple dosing at 2 mg b.d., which was approximately 20 % lower than following the single 2 mg rectal dose on Day 1 (p=0.006).

Results were also provided from a second analysis of the 8 am cortisol levels as this has been traditionally used to monitor systemic effects of glucocorticoids. No statistically significant differences in 8 am levels were found. However, this is known to be a less sensitive marker and regression analysis showed a linear decrease of morning cortisol values from Day 1 to Day 5 (Figure 6).

Effect on blood lymphocyte and granulocyte counts

The changes in lymphocyte and granulocyte counts on Day 1 (15 ± 12% decrease in lymphocytes; 17 ± 17% increase in granulocytes) were comparable to the changes at Day 5 (15 ± 15% decrease in lymphocytes; 20 ± 19% increase in granulocytes). The maximal effects (based on % of leucocytes) were observed 3 to 6 h following rectal administration of budesonide (Figure 7).

Figure 5. Mean concentration time curve for cortisol – Study BUF-7/BIO

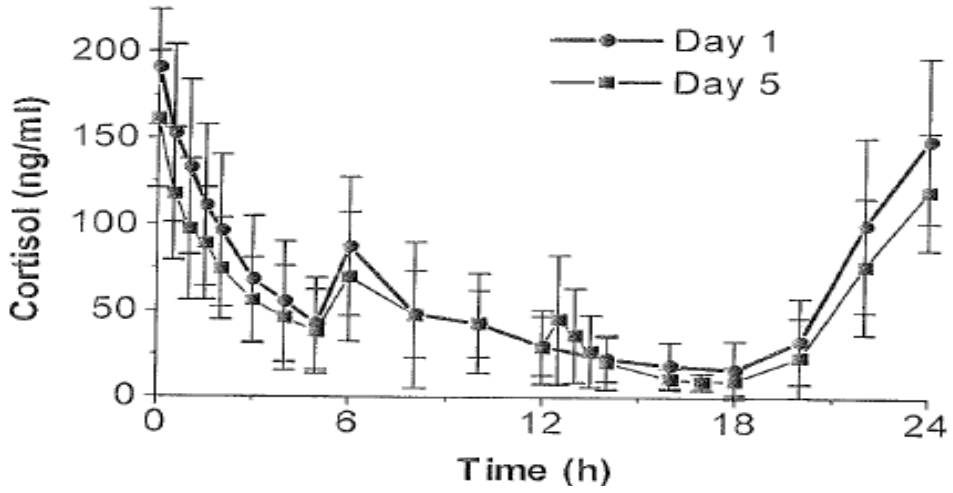


Figure 6. Serum cortisol levels after rectal Budenofalk 2mg for 5 days – Study BUF-7/BIO. Regression lines based on morning cortisol levels.

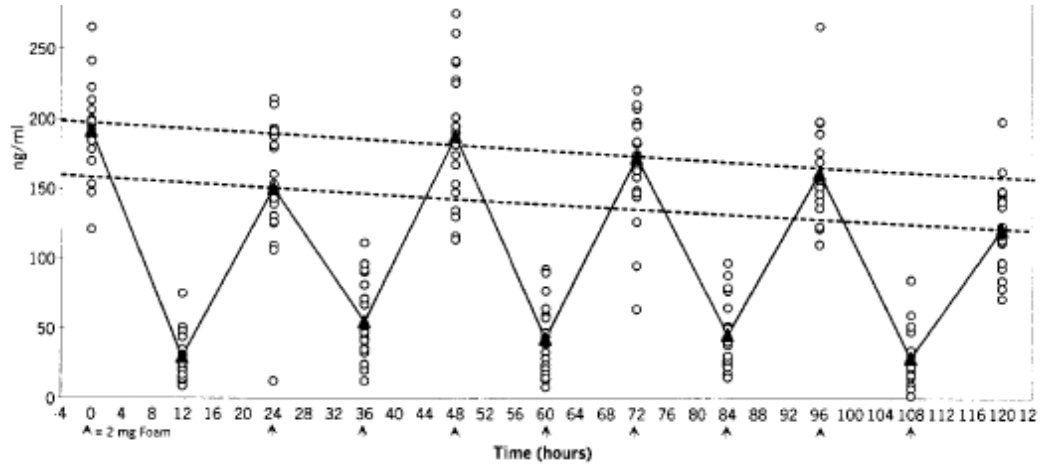
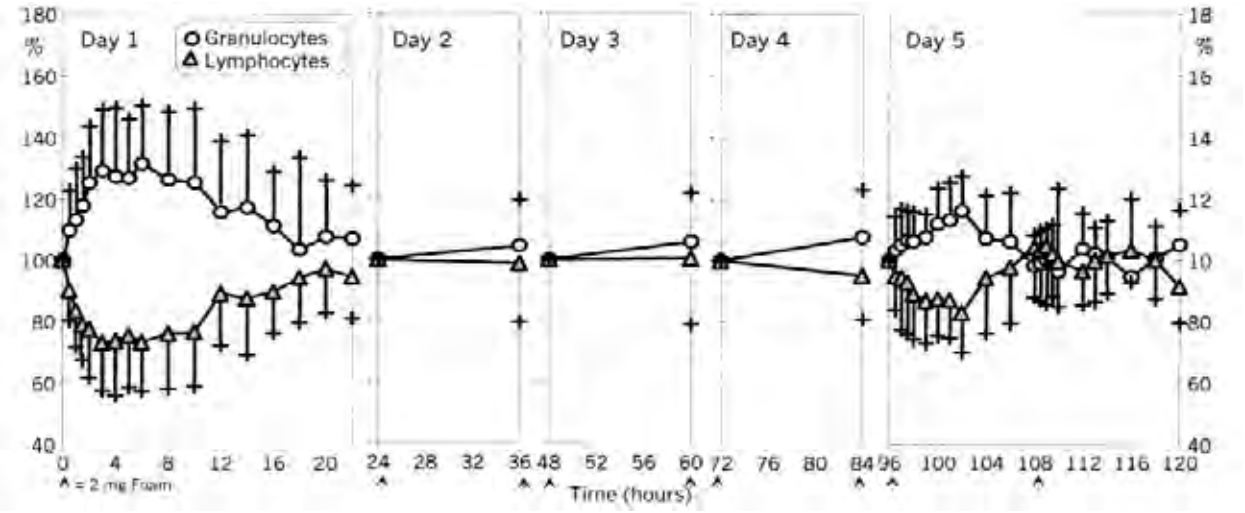


Figure 7. Mean % granulocyte and lymphocyte counts – Study BUF-7/BIO



Study BUF-5/UCA. Pharmacodynamic dose-response of rectally administered budesonide in patients with active ulcerative colitis

This dose finding study is described and critiqued in more detail above. Additional aspects of the safety evaluation in this study are discussed at *Safety* below.

Systemic pharmacodynamic effects of thee rectal doses of Budenofalk foam enema (budesonide 0 mg (placebo), 2 mg and 4 mg) given over a 6 week period to patients with mild to moderate active ulcerative colitis were monitored as part of the evaluation of safety as follows:

HPA axis:	serum cortisol and aldosterone levels at baseline and 42 days
	serum electrolytes (e.g. potassium) at baseline, 14, 28 and 42 days.
Immune system:	lymphocyte and granulocyte counts at baseline, 14, 28 and 42 days
	C-reactive protein (CRP) as a marker of systemic inflammatory activity at baseline, 14, 28 and 42 days.

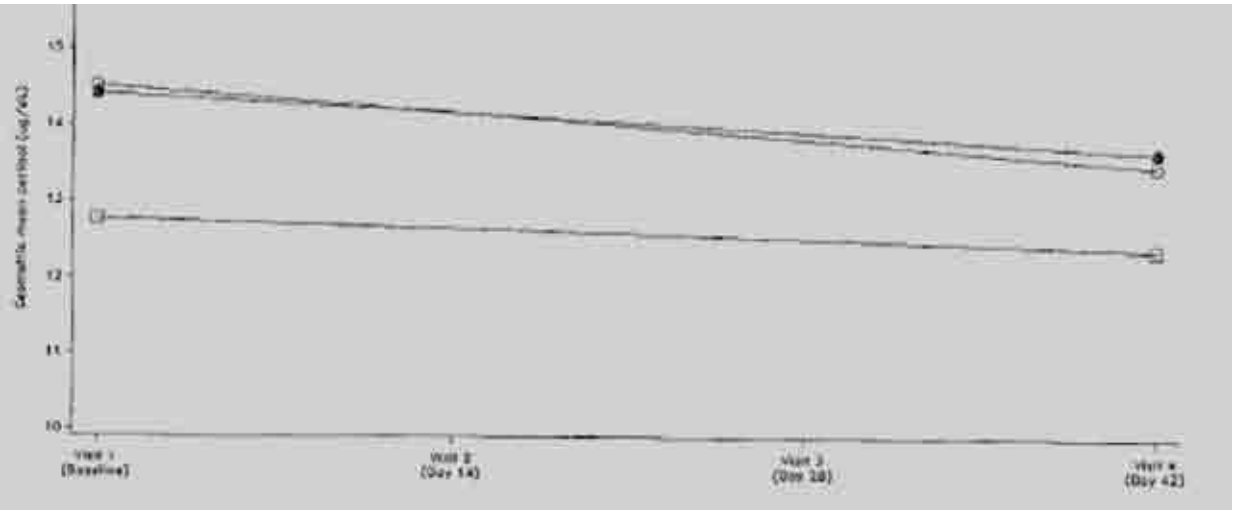
Samples were assayed for cortisol, CRP, aldosterone and electrolyte levels at a central laboratory. Results presented below were derived from the ITT population unless indicated otherwise.

Effect on serum cortisol

Serum cortisol levels were log transformed and the geometric mean was calculated with 95% confidence intervals. There was a small reduction in cortisol levels in all treatment groups. The geometric means of the serum cortisol levels were calculated for each treatment group at Day 1 and Day 42 and are shown in Figure 8.

There were no statistically significant differences between either of the budesonide treatment groups and placebo with respect to cortisol levels at Day 42 (Visit 4) using the LOCF. Also, at Day 42 the number of patients with clinically significant decreased cortisol levels (again using the LOCF) were similar in the thee groups, with 4 (5 %), 5 (7%) and 3 (4%) in the placebo, budesonide 2 mg, budesonide 4 mg groups, respectively (Fisher exact test p values for comparison with placebo were 0.957 and 1.000 for the budesonide 2 mg and 4 mg groups, respectively). At baseline, the corresponding number of patients with clinically significantly decreased serum cortisol level had been 4 (5 %), 0 and 3 (4 %) in the budesonide 4 mg, budesonide 2 mg and placebo group, respectively. A clinically significantly decreased plasma cortisol level was defined as a serum cortisol level <5.4 µg/dL.

Figure 8. Geometric mean cortisol levels – Study BUF-5/UCA



● Placebo ○ Budesonide 2mg □ Budesonide 4mg

Similar results were observed in each treatment group when only those patients with results at Visit 4 were analysed, indicating no bias had been introduced though missing data and/or patient withdrawals.

Effect on aldosterone and electrolyte levels

Changes in aldosterone and electrolyte levels are summarised in Table 8. Of particular note, the mean baseline aldosterone level in the placebo group was above the upper limit of the normal range of 10-160 ng/mL, whereas the levels for the budesonide groups were within the normal range. By the end of 6 weeks treatment the mean aldosterone level in the placebo group had decreased but remained slightly above the normal range. However, it can be appreciated that for all groups there was considerable inter individual variation in levels at baseline, with each group having maximal values well outside the normal range. Coefficients of variation (calculated by the clinical evaluator from SD/mean) were 134%, 59% and 147% for the placebo, budesonide 2 mg and budesonide 4 mg groups, respectively, indicating considerable dispersion of the individual levels. Although not shown in the table (8), in all 3 groups the median values were below the mean values (132, 130 and 106 ng/L for the placebo, budesonide 2 mg and budesonide 4 mg groups, respectively). This indicates the distributions at baseline were right skewed by a small

number of large values. In such a setting it is more appropriate to consider changes in median values. The median levels of aldosterone were within normal range for all treatment groups at baseline and remained there during treatment. At Day 42 the corresponding median values were 123, 123 and 112 ng/L.

Table 8. Effects on aldosterone and serum electrolyte levels* - Study BUF-5/UCA

	placebo n=76	budesonide 2mg n=70	budesonide 4mg n=76
Aldosterone ng/L			
Baseline at visit 1:mean (range)	188 (13-2000)	146 (13-478)	147 (13-2000)
End of treatment at visit 4: mean (range)	169 (13-890)	151 (13-456)	157 (13-1000)
Chloride (mmol/L)			
Baseline at visit 1:mean (range)	105 (95-114)	105 (93-115)	106 (95-115)
End of treatment at visit 4: mean (range)	106 (94-115)	106 (96-114)	106 (87-114)
Potassium (mmol/L)			
Baseline at visit 1:mean (range)	4.4 (3.4-5.9)	4.3 (3.3-5.3)	4.4 (3.7-5.7)
End of treatment at visit 4: mean (range)	4.4 (3.2-5.9)	4.6 (3.1-22.9)	4.7 (3.4-25.8)
Sodium (mmol/L)			
Baseline at visit 1:mean (range)	142 (132-151)	141 (127-150)	141 (135-154)
End of treatment at visit 4: mean (range)	141 (123-147)	141 (131-149)	141 (128-149)

* Normal ranges: aldosterone 10-160 ng/l; chloride 98-107 mmol/l; potassium 3.6-5.0 mmol/l; sodium 135-145 mmol/l

Mean baseline levels of the serum electrolytes were within the normal range for all treatment groups and showed virtually no changes at the end of treatment (Day 42/Visit 4) in any of the treatment groups.

Evaluator's comment

Although the protocol required serum electrolytes to be examined routinely at all four visits, it is apparent that few (between 1 and 3) patients in any group had levels taken at Visits 2 and 3. The reasons for this deviation from the protocol were not stated and, indeed, there was no mention of this in within the study report. Presumably it was considered that electrolyte changes needed to be examined in the context of the overall mineralocorticoid effects (that is, in conjunction with aldosterone levels) and given that aldosterone was only assessed at baseline and Visit 4, there was little point in assessing electrolyte levels otherwise. However, electrolyte monitoring is a key part of the basic monitoring of safety in clinical trials and changes in electrolyte levels taken at Visits 2 and 3 could have been an early indicator of any unanticipated adverse effects on these or other parameters.

Note: In its response to the first round evaluation report, the sponsor confirmed electrolytes were not measured at Vvisits 2 and 3, in keeping with the monitoring of aldosterone levels. The sponsor noted that more intensive monitoring of electrolytes was performed in Sstudies BUF-6/UCA and BUF-9/UCA

Effect on immunocompetent blood cells

Summary statistics for lymphocyte and granulocyte counts were presented for each visit. No appreciable changes in lymphocyte or granulocyte counts were observed. These have been summarised by the clinical evaluator in Tables 9 and 10.

Effect on C-Reactive Protein (CRP)

At baseline the CRP was slightly lower for the budesonide 4 mg group (geometric mean [95%CI] 3.4 mg/L [2.7 – 4.3 mg/L] compared to 4.5mg/L [3.5 – 5.9 mg/L] in the placebo group and 4.6 mg/L [3.5 – 6.0 mg/L] in the budesonide 2 mg group. The median level of 1.8 mg/L was also considerably lower than in the other groups (1.8 mg/L versus 4.6 and 4.4 mg/L, respectively). At the end of 6 weeks treatment (LOCF), the geometric mean values had fallen in all 3 groups to comparable levels (geometric mean [95%CI] of 3.5 mg/L [2.7 – 4.4 mg/L] for placebo, 3.6 mg/L [2.7 – 4.8 mg/L] for budesonide 2 mg and 3.3 mg/L [2.6 – 4.2 mg/L] for budesonide 4 mg). Median levels were 1.8 mg/L in all thee

groups. There was no statistically significant differences in the mean ratio of CRP concentrations at 42 days and baseline between placebo and either budesonide 2 mg (least squares geometric mean ratio to placebo 0.99, p=0.972) or budesonide 4 mg (LSGM ratio to placebo 1.12, p=0.464).

Table 9. Effect of Budenofalk foam on lymphocyte counts – Study BUF-5/UCA

		Placebo	BUD 2mg	BUD 4mg
Visit 1 (Baseline)	n	76	69	76
	Mean ± SD	29 ± 9.0	30 ± 7.5	30 ± 8.5
	Median	30	29	29
	Range	12 – 59	16 – 55	13 – 45
Visit 2	n	75	70	76
	Mean ± SD	30 ± 7.0	32 ± 8.7	30 ± 8.9
	Median	30	30	30
	Range	18 – 50	15 – 59	9 – 54
Visit 3	n	72	67	74
	Mean ± SD	31 ± 9.3	31 ± 8.4	32 ± 9.8
	Median	31	32	32
	Range	14 – 58	15 – 50	11 – 57
Visit 4	n	68	62	71
	Mean ± SD	31 ± 9.3	29 ± 9.2	32 ± 9.9
	Median	30	28	30
	Range	9 – 55	10 – 54	15 – 59
Visit 4 % change from baseline	n	68	61	71
	Mean ± SD	10 ± 41.8	4 ± 37.6	15 ± 50.6
	Median	0	-7	3
	Range	-64 – 156	-64 – 116	-53 – 269

Table 10. Effect of Budenofalk foam on granulocyte counts – Study BUF-5/UCA

		Placebo	BUD 2mg	BUD 4mg
Visit 1 (Baseline)	n	76	69	76
	Mean ± SD	62 ± 8.7	62 ± 8.0	63 ± 8.6
	Median	63	62	64
	Range	37 – 86	37 – 78	45 – 80
Visit 2	n	75	70	76
	Mean ± SD	62 ± 7.5	60 ± 10.3	63 ± 9.5
	Median	62	61	62
	Range	39 – 84	7 – 78	41– 86
Visit 3	n	72	67	74
	Mean ± SD	60 ± 11.5	61 ± 8.5	61 ± 10.5
	Median	62	61	64
	Range	8 – 78	40 – 82	38-85
Visit 4	n	68	62	71
	Mean ± SD	62 ± 9.2	62 ± 9.5	61 ± 10.2
	Median	62	63	62
	Range	39 – 87	31 – 82	40 – 78
Visit 4 % change from baseline	n	68	61	71
	Mean ± SD	3 ± 21.2	2 ± 18.8	-2 ± 19.2
	Median	2	0	-3
	Range	-38 – 78	-42 – 68	-50 – 49

Evaluator's comment

Examination of the residuals from an analysis of untransformed CRP data indicated the distribution did not follow a normal distribution. Consequently, the data were log-transformed to provide geometric means and ratios with the baseline value. This was considered appropriate. Levels were said to have been determined at each visit. However, summary statistics were only provided for baseline and Visit 4 and it is not clear if assays of CRP were in fact performed at Visits 2 and 3.

Note: In its response to the first round evaluation report, the sponsor confirmed CRP levels were not measured at Visits 2 and 3.

Study BUF-6/UCA. Systemic pharmacodynamics of rectally administered budesonide 2 mg o.d. in active distal ulcerative colitis patients

The study is described and critiqued in more detail under *Efficacy* below. Additional aspects of the safety evaluation in this study are discussed under *Safety* below.

Two of the objectives of this prospective, active controlled, multicentre, randomised, open label, parallel group trial were to show that 8 weeks of treatment with Budenofalk foam enema (BUF) 2 mg od in patients with proctitis or proctosigmoiditis was safe and that BUF had improved safety and tolerability compared to hydrocortisone acetate (HCA), based on the lack of systemic side effects.

Systemic pharmacodynamic effects on the HPA axis and bone metabolism were monitored as part of the evaluation of safety. Samples were collected for determination of serum cortisol levels at baseline (Day 0) and Days 14, 28 and 56 (final visit) and for determination of bone-specific alkaline phosphatase and osteocalcin levels at baseline (Day 0) and Days 28 and 56 (final visit). Samples were assayed at a central laboratory.

All 3 parameters were found to be log normally distributed and were thus log transformed. The geometric means at each visit and geometric mean change from baseline and corresponding 95% confidence intervals were calculated. Comparisons between BUF and HCA foam were made using Fisher's exact test. Ninety-five percent confidence intervals for the ratio (of the geometric mean difference from baseline) for BUF compared to HCA were generated. Log transformed data was back transformed to provide a ratio to hydrocortisone acetate on the original scale, for each variable. Results presented below were derived from the ITT (safety) population unless indicated otherwise.

Effects on serum cortisol

At baseline, the geometric mean serum cortisol levels were similar across the treatment groups - 13.3 µg/dL (95% CI: 12.2 – 14.5) for BUF patients and 12.7 µg/dL (95% CI: 11.5 – 14.0) for the HCA group. At the last visit, using LOCF, the geometric means had decreased slightly in the BUF group to 13.1 µg/dL (95% CI: 11.8 – 14.5) and increased in the HCA group to 13.5 µg/dL (95%CI: 12.3 – 14.8). The ratio to baseline values at each visit is shown in Table 11. Statistical analysis using analysis of variance (ANOVA) adjusted for baseline values and country found no statistically significant difference between the two groups at the last visit (LOCF) in respect of the geometric mean ratios to baseline (p=0.503).

Table 11. Effect of Budenofalk on cortisol levels – ratio of each visit to baseline – Study BUF-6/UCA

	Budesonide 2 mg n = 120				Hydrocortisone acetate 100 mg n = 128			
Study day	14	28	56	LOCF	14	28	56	LOCF
Cortisol ratio to baseline								
Number of patients with data at that visit	109	100	69	112	117	101	66	120
Geometric mean	0.85	0.98	1.03	0.99	1.02	1.02	1.05	1.07
95% CI for geometric mean	(0.77, 0.94)	(0.88, 1.08)	(0.91, 1.16)	(0.89, 1.10)	(0.91, 1.14)	(0.90, 1.15)	(0.95, 1.17)	(0.95, 1.20)
Least squares mean [1] Ratio to hydrocortisone acetate 95% CI				1.01 0.96 p = 0.503 (0.92, 1.10)				1.05
Analysis excluding out-liers [2]								
Least squares mean [1] Ratio to hydrocortisone acetate 95% CI				1.03 0.95 p = 0.384 (0.95, 1.11)				1.08

Effects on bone metabolism

Osteocalcin levels increased steadily over time in both treatment groups. The geometric mean osteocalcin levels were slightly lower in the BUF group thoughout the study compared to the HCA group. At Visit 4 (Day 56 [LOCF]), the least squares geometric mean estimate of the ratio to baseline was l.06 (95% CI: 0.98 - l.l6) in the BUF group and 1.18 (95% CI: 1.08 - 1.28) in the HCA group. The difference in ratios was not statistically significant (p=0.088).

Bone specific alkaline phosphatase (bAP) levels increased in both treatment groups over the treatment period and the geometric means were marginally lower in the BUF group thoughout the study. At Visit 4 (Day 56 (LOCF), the least squares geometric mean ratio to baseline was 0.99 (95% CI 0.95 - 1.02) in the BUF group and 1.03 (95% CI: 0.99 - 1.07) in the hydrocortisone group. There was no evidence of a statistically significant difference in ratio to baseline for the two groups (p=0.l08).

Evaluator's comments

Of particular note in this study was the number of discontinuations prior to the last visit; 31 (26%) patients in the BUF group and 42 (33%) patients in the HCA group, which resulted in 89 patients in the BUF group and 86 in the HCA group. However, serum cortisol, osteocalcin and bAP data were available for only 60-70 patients in each group, depending on the parameter measured, so there was a significant amount of missing data. However, similar results were observed in each treatment group when only those patients with results at Visit 4 were analysed, indicating no bias had been introduced though missing data and/or patient discontinuations.

In order to control for natural diurnal variation in serum cortisol levels, a standard time period was quite appropriately specified for the collection of samples for assay. However, the study report was confusing in that it cited two different time periods for sample collection: 8:00 am to 10:00 am and 7:30 am to 10:30 am. The protocol specified 8:00 am to 10:00 am.

The specified time period for collection of samples for serum cortisol quantification was not adhered to for all patients. Consequently, an analysis of samples that were said to have been collected within the correct time frame was also presented but this analysis was reportedly of samples taken between 7:30 am and 10:30 am. This gave very similar results to the ITT analysis; the cortisol ratio to baseline geometric means at last visit (LOCF) was 1.00 (95% CI: 0.90 – 1.11) for BUF and 1.06 (95% CI: 0.95 – 1.19) for HCA with a ratio of BUF to HCA of 0.96 (p=0.453, ANOVA adjusted for baseline value and country).

A clinically significant decrease in serum cortisol was originally defined in the protocol as a level <5.4 µg/dL. However, the laboratory normal range for serum cortisol was 5.0 – 25 µg/dL, with serum cortisol values recorded as whole numbers. Therefore, a secondary analysis was performed to identify those patients who recorded serum cortisol values of < 5 µgLdl, as it was considered that such an analysis would give a more realistic figure for clinically significantly decreased serum cortisol. This approach is considered to have been acceptable.

It was noted that the a sample size of 240 patients (120 per treatment group) provided at least 80% power to detect a difference of 0.163 in log serum cortisol levels (corresponding to a ratio of geometric means of 0.85), assuming a standard deviation in log serum cortisol levels of 0.35 and a two-sided 5% statistical significance level. Thus, the study had 80% power to detect a 15% decrease or an 18% increase in serum cortisol levels for one treatment group in comparison to the other

Study BUF-9/UCA. Systemic pharmacodynamics of rectally administered budesonide 2 mg o.d. in patients with active distal ulcerative colitis

The study is described and critiqued in more detail under *Efficacy* of this evaluation report

Serum cortisol levels and the proportion of patients with cortisol deteriorations (below normal range) were measured to assess the degree of adrenal and pituitary suppression in patients who received a daily dose of 2 mg rectal budesonide for 4 weeks, administered either as a liquid enema (Entocort, AstraZeneca (EBE), n=268) or as foam (Budenofalk (BUF), n=265). Levels were assessed at baseline and the final visit at Week 4. Samples were analysed at a central laboratory.

Summary statistics are shown in Table 12. The geometric mean serum cortisol levels for the BUF group rose slightly during treatment from 14.35 µg/dL at baseline to 14.84 µg/dL at 6 weeks. The absolute change from baseline was distributed symmetrically and could be better described by the arithmetic instead of the geometric mean; the mean change from baseline was 0.41 µg/dL (95% CI: -0.61 to 1.43). The absolute change from baseline for the EBE group was -0.20 µg/dL (95% CI: -1.22 to 0.81).

Deterioration of serum cortisol levels below the normal range (< 5.435 µg/dL) were found in 3 (1%) patients in the BUF group and 2 (1%) patients in the EBE group. However, of the 3 BUF patients, 2 had samples collected outside the specified time window of 7 am to 9 am. When patients whose samples were not compliant with the time window for collection were excluded from the analysis, the mean changes from baseline were 1.10 µg/dL (95% CI: 0.03 – 2.18) for the BUF group and -0.06 µg/dL (95% CI: -1.18 – 1.07) in the EBE group.

Table 12. Summary statistics for cortisol – Study BUF-9/UCA

	Budenofalk foam				Budenofalk enema			
	All samples		7am-9am samples		All samples		7am-9am samples	
Visit	1 (n=257)	3 (n=248)	1 (n=196)	3 (n=211)	1 (n=253)	3 (n=248)	1 (n=198)	3 (n=212)
Geometric mean [95% CI]	14.4 [13.5;15.3]	14.8 [14.0; 15.8]	14.2 [13.2; 15.2]	15.6 [14.7; 16.5]	14.4 [13.5; 15.4]	14.5 [13.6; 15.4]	14.9 [13.9; 15.9]	14.8 [13.8; 15.7]
Pts with cortisol <5.4µg/dL	7 (3%)	4 (2%)	6 (3%)	2 (1%)	5 (2%)	4 (2%)	4 (2%)	3 (1%)
mean Δ [95% CI]		0.41 [-0.6;1.43]		1.10 [0.03; 2.18]		-0.20 [-1.22;0.81]		-0.06 [-1.18; 1.07]

Summary of Pharmacodynamics

The information in the following summary is focused on effects following rectal administration of budesonide using Budenofalk foam enema. Information pertaining more generally to the use budesonide is covered in the CER for the Budenofalk oral capsules.

Mechanism of action

The mechanism of action of budesonide was discussed in the CER for Budenofalk oral capsules.

Pharmacodynamic effects

Primary pharmacodynamic effects

Budesonide is a topically active drug, which does not require systemic absorption for its primary pharmacodynamic activity. The primary pharmacodynamic effect for the treatment of ulcerative colitis is considered to be anti-inflammatory activity within the distal intestinal wall where it is taken up by cells in the mucosa and submucosa.

This has been investigated using *in vivo* animal models for ulcerative colitis. According to the sponsor, appropriate *in vivo* models for evaluation of the effects of budesonide on intestinal inflammation are rat models of ulcerative colitis and a hamster model of ileitis induced by local (intra colonic or intra rectal) application of acetic acid or 2,4,6-trinitrobenzene sulfonic acid. The resulting colitis showed clinical and pathological similarities to human ulcerative colitis, with diarrhoea, mucosal damage, inflammation and ulceration, increased plasma exudation, and increased mucosal neutrophil and macrophage infiltration.

Reportedly, animal studies have consistently shown that budesonide dose dependently prevents the induction of colitis and reduces pathological damage in the colon, including a reduction in ulceration; reduces plasma exudation into the colon; decreases neutrophils (myeloperoxidase activity) and macrophages in the colon; reduces damage to enteric nerves; and reduces diarrhoea. Budesonide was found to be effective when administered locally (directly into the colon) or subcutaneously. Budesonide also reduced plasma exudation into the gut in another model of allergen-induced vascular permeability in rats.

Secondary pharmacodynamic effects

The sponsor noted that a secondary effect of corticosteroids on electrolyte transport may confer additional benefit in the treatment of ulcerative colitis via an anti-diarrhoeal effect that has been demonstrated in *in vivo* animal studies (nonclinical data). Dexamethasone was reported to have been shown to stimulate electrogenic sodium (Na^+) transport and water absorption in the distal segment of rat colon but not the proximal colon. Specifically with respect to budesonide, in another study both dexamethasone and budesonide were found to increase expression and activity of the Na^+/hydrogen (H^+) and chloride (Cl^-)/bicarbonate ($HCO3^-$) exchangers in rat cholangiocytes, suggesting budesonide could potentially have a similar effect in the distal colon to that of dexamethasone.

As glucocorticoid receptors are expressed in virtually all cells, the pleiotropic effects of glucocorticoid receptors on multiple signalling pathways are responsible for the unwanted systemic side effects associated with glucocorticoid therapy. In addition to the anti-inflammatory activity, glucocorticoid effects include gluconeogenesis, proteolysis and lipolysis and adverse bone metabolism effects (osteoporosis and osteonecrosis), amongst others. Some glucocorticosteroids also have mineralocorticoid effects such as sodium and water retention and potassium loss. Furthermore, the HPA axis plays a central role in regulating glucocorticoid receptor signalling though the endogenous natural glucocorticoid, hydrocortisone. Exogenous corticosteroids exert negative feedback on the HPA axis, resulting in decreased adrenocorticotrophic hormone (ACTH) and adrenal suppression, reflected in decreased cortisol

levels, particularly with repeated high doses. This manifests as an inability to mount suitable responses to stresses such as infection and trauma.

Budesonide should theoretically have fewer systemic side effects because of its high first pass metabolism. However, when administered rectally, budesonide may pass into the venous circulation via the rectal plexus, thereby avoiding first pass metabolism and increasing systemic bioavailability.

Effects of rectally administered budesonide on serum cortisol levels as a measure of HPA axis suppression

No clinically significant decreases were seen in mean morning serum cortisol levels in comparison to baseline when budesonide was administered to patients with distal ulcerative colitis at a dose of 2 mg once daily for 4 weeks (BUF-9/UCA), 6 weeks (BUF-5/UCA) or 8 weeks (BUF-6/UCA). Also very few patients developed cortisol levels below the normal range during treatment.

Dose dependency of HPA axis suppression with budesonide was examined in patients with ulcerative colitis in a single study of 6 weeks duration (BUF-5/UCA). In this study small decreases in morning serum cortisol levels were observed in the placebo, budesonide 2 mg and budesonide 4 mg groups but there were no statistically significant differences between the budesonide groups and placebo.

In healthy volunteers, budesonide foam enema at a dose of 2 mg bdfor 5 days was associated with a 20% decrease in 24 h serum cortisol levels compared to a single 2 mg dose.

Effects on serum aldosterone and serum electrolyte levels

Rectal administration of budesonide at doses of 2 mg or 4 mg daily for 6 weeks had no effects on serum aldosterone or serum electrolyte levels (BUF-5/UCA).

Effects on bone metabolism

Budesonide 2 mg given rectally once daily for 8 weeks to patients with ulcerative colitis was observed to have no effect on serum bone-specific alkaline phosphatase and serum osteocalcin levels (BUF-6/UCA).

Time course of pharmacodynamic effects

No data were presented regarding the time course of primary pharmacodynamic effects. No clinically significant systemic pharmacodynamic effects were observed with respect to serum cortisol, serum bone-specific alkaline phosphatase and serum osteocalcin levels with 2 mg rectal doses of budesonide for up to 8 weeks. No effect was observed on serum aldosterone or serum electrolyte levels with dosing at 4 mg for 6 weeks.

Relationship between drug concentration and pharmacodynamic effects

No data were submitted.

Genetic, gender and age related differences in pharmacodynamic response

No data were submitted.

Pharmacodynamic interactions

This was discussed in the CER for Budenofalk oral capsules.

Evaluator's overall conclusions on pharmacodynamics

The focus of this application was to show that budesonide administered rectally at a dose of 2 mg once daily was not associated with clinically significant systemic pharmacodynamic effects that could give rise to side effects. No statistically or clinically significant effects were seen on

serum cortisol levels and bone metabolism markers in patients with dosing at the proposed regimen for up to 8 weeks. Furthermore, no effect on serum aldosterone or electrolyte levels was observed with the proposed dosing regimen for 6 weeks.

In Study BUF-7/BIO the 24 h serum cortisol profile ($AUC_{0 \text{ to } 24}$) was assessed in healthy volunteers with single and multiple dosing. This demonstrated a 20% decrease in 24 h serum cortisol levels after dosing at 2 mg bd (that is, higher than the recommended dose) for 4 days compared to a single 2 mg dose.

None of the studies incorporated a pharmacodynamic variable as its primary endpoint and consequently the sample size and power of these studies were not geared toward finding differences in these variables. Also, it is of note that the monitoring of the effect on cortisol levels was suboptimal. With the exception of Study BUF-7/BIO, the assessment of the effect of rectally administered budesonide on cortisol was limited to the monitoring of morning serum cortisol levels and the proportion of patients who developed serum levels below the lower limit of the normal range. Urinary (24 h) cortisol excretion, ACTH levels and ACTH testing were not performed in any of the studies.

Monitoring of morning serum cortisol levels is known to be a less sensitive indicator of HPA axis suppression, so it is perhaps not surprising that no effects were found even with the dose finding study, which used a dose of 4 mg daily for 6 weeks. A case in point is the dose response study for budesonide enema (Entocort) reported by Hanauer et al 1998[18], which found a statistically significant difference from placebo (n=59) in the mean basal cortisol levels after 6 weeks with budesonide 8 mg daily (n=60) but not with budesonide 0.5 mg (n=57) or 2.0 mg daily (n=55). However, a statistically significant difference from placebo was also found with budesonide 2 mg when ACTH stimulated cortisol was measured.

Ideally, ACTH stimulated cortisol levels should have been used in an attempt to elucidate a dose related effect for budesonide. However, reassurance can be taken from the fact that there were few adverse drug reactions consistent with known corticosteroid side effects in the BUF clinical development program.

Dosage selection for the pivotal studies

The sponsor nominated two studies as being pivotal to the application; Studies BUF-9/UCA and BUF-6/UCA. The choice of dosage regimen of 2 mg once daily in both these studies was based on the results of dose finding studies reported in the published literature as follows:

- A trial by the Danish Budesonide Study Group 1991[19] compared treatment with budesonide 1 mg/day, 2 mg/day and 4 mg/day against prednisolone 25 mg/100 mL daily as a positive control for the treatment of distal ulcerative colitis. Budesonide 2 and 4 mg/day were as effective as prednisolone in improving clinical symptoms and proctoscopy findings but not at a dose of 1 mg/day. The particular budesonide formulation used was that of a liquid enema, with tablets being dispersed immediately before use. Treatment was only continued for 2 weeks;
- A dose-finding study by Hanauer et al, 1998[18] of placebo enemas and Entocort budesonide liquid enemas at 0.5 mg/100mL, 2.0 mg/100mL and 8.0 mg/100mL for a period of 6 weeks found budesonide 2 mg/100mL once daily was the lowest effective dose. The 2 mg dose was not statistically significantly different from the 8 mg dose. However, the clinical evaluator

[18] Hanauer SB, Robinson M, Pruitt R, et al (Budesonide Enema Study Group). Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis - A dose-ranging study. *Gastroenterology* 1998; **115**: 525 -32.

[19] Danish Budesonide Study Group. Budesonide enema in distal ulcerative colitis – a randomized dose-response trial with prednisolone enema as positive control. *Scand J Gastroenterol* 1991; 26: 1225 -30.

noted that that particular study was not designed to detect a difference between those two doses; and

- A study by Lindgren et al 1997[20] showed budesonide (Entocort enema) at a dose of 2 mg bdwas no more effective at inducing clinical remission in patients with ulcerative colitis at 4 and 8 weeks than at a dose of 2 mg od

Evaluator's comment:

None of these studies was conducted using Budenofalk foam enema. Furthermore, the sponsor's own dose finding study (BUF-5/UCA) failed to show a difference between either budesonide 2 mg/day or 4 mg/day and placebo in any of the efficacy parameters examined. Of particular note in that study was that a high proportion of patients achieved remission in all groups and the placebo response (61%) was much higher than the expected spontaneous remission rate which had been based on rates reported in the published literature. This study is presented in more detail below.

Efficacy

Treatment of active distal ulcerative colitis

Pivotal efficacy studies

Study BUF-9/UCA

Study design, objectives, locations and dates

Study BUF-9/UCA was a double blind, double dummy, randomised, multicentre, comparative study of the efficacy and tolerability of Budenofalk foam (2 mg/25 mL) (BUF) and Entocort (budesonide) enema (2 mg/100 mL) (EBE) in patients with active ulcerative proctitis or proctosigmoiditis. The study was conducted at 52 centres in 7 countries (6 in Europe and 1 in Israel) over the period February 2001 to March 2003.

Inclusion and exclusion criteria

Adult patients aged 18 to 70 years with an established or new diagnosis proctitis or proctosigmoiditis and a Clinical Activity Index (CAI) >4 and ≤ 12, and an Endoscopic Index≥ 4 were eligible for study entry. Key exclusion criteria were infectious bowel disease, newly occurring colitis with symptoms present for < 2 weeks, a history of Crohn's disease or prior bowel operation; toxic megacolon; present or past colorectal cancer; symptomatic gastrointestinal disease; oral or rectal steroids within 1 month prior to baseline; immuno-suppressants within 3 months prior to baseline; or long-term NSAID treatment.

Evaluator's comment

It is not clear whether the patients were recruited from hospital in patients, outpatients, specialist clinics, general practice or a combination of these sources. This is important from the perspective of assessing the generalisability and validity of the study results, particularly noting the placebo response rate in Study BUF-5/UCA which included a large proportion of hospitalised patients was much higher than expected and at 61% was similar to the expected rate for the budesonide preparations in this study.

Note: In its response to the first round evaluation report the sponsor confirmed that patients were recruited from both hospitals and private gastroenterologist practices. Thus, the results can be readily generalised to everyday usage.

[20] Lindgren S, Suh O, Persson T, Pantzar N. Treatment of active distal ulcerative colitis (UC) and maintenance of remission with Entocort enema: A randomised controlled dosage study. *Gut* 1997; 41(Suppl. 3): A223.

Study treatments and blinding methods

Patients received either Budenofalk foam (one actuation generating a volume of approximately 25 mL containing 2 mg budesonide) and placebo enema, or placebo foam and Entocort enema (100 mL liquid containing 2 mg budesonide) for 4 weeks according to a randomisation list. The placebo foam was identical to Budenofalk foam with respect to volume and appearance. Similarly, the tablet that was dispersed to create the placebo enema was the same size and appearance as the tablet component of the Entocort enema.

As a consequence of the double dummy design and the fact that the rectal foam and the enema could not be administered at the same time, one medication was administered in the morning and the other in the evening. To avoid bias associated with the time of administration, patients were stratified to either administer the foam in the morning and the enema in the evening (sequence "f") or the other way around (sequence "e").

Efficacy variables and outcomes

The main efficacy variable was the Clinical Activity Index (CAI) according to Rachmilewitz 1989[21], which was calculated as the sum of scores of the following seven parameters:

- Number of stools
- Number of bloody stools
- Severity of abdominal pain/cramps
- General well being
- Temperature
- Extra-intestinal disease manifestations
- erythrocyte sedimentation rate (ESR) and haemoglobin levels

The CAI was calculated at each visit. Data for the first four variables were taken from entries in the patient's diary for the last 7 days before the visit (with retrospective completion by the patient at the baseline visit). The last thee variables were determined at the day of the visit by the investigator or, in the case of ESR and haemoglobin (Hb), from laboratory analyses.

Other efficacy variables included:

- The Disease Activity Index (DAI) as defined by Sutherland 1987[22], based on stool frequency, rectal bleeding, mucosal appearance and the physician's rating of disease activity
- Endoscopic Index according to Rachmilewitz 1989
- Histological Index according to Riley et al 1991[23]
- Physician's Global Assessment (PGA): a six point scale of the physician's rating of changes in the patient's symptoms.

The primary efficacy endpoint was clinical remission, defined as a CAI ≤ 4 at the final/ discontinuation examination. If a patient discontinued the study prematurely, the last value on

[21] Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ* 1989; 298: 82-86.

[22] Sutherland LR, Martin F, Greer S, et al. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology* 1987; 92: 1894-8.

[23] Riley SA, Mani V, Goodman MJ, et al. Microscopic activity in ulcerative colitis: What does it mean? *Gut* 1991; 32: 174-8.

study medication was used (LOCF) but if no CAI under study medication was recorded, no clinical response was assumed.

Secondary efficacy endpoints assessed at the final or withdrawal visit included: change in CAI; change in number of stools per day; change in number of bloody stools per day; time to first clinical remission; change in DAI; clinical remission based on DAI (DAI ≤ 3); endoscopic remission (EI < 4); histological improvement; therapeutic success and benefit based on global assessment (PGA); and patient acceptance of the study drug. Note: For the time to first clinical remission, remission was not based on the CAI but rather was defined as no more than thee daily bowel movements without blood.

The determination and/or calculation of the various disease activity and endoscopic indices used in this study are summarised in Table 13.

Table 13. CDAI, DAI, EI and HI score calculations - Study BUF-9/UCA

The values for the calculation of the CAI (① - ⑦)	Score
① Number of stools weekly:	
< 18	0
18 - 35	1
36 - 60	2
> 60	3
② Blood in or on the stools (on a weekly basis):	
none (0-1 stool)	0
a little (≤30% of all stools)	2
a lot (>30% of all stools)	4
③ Abdominal pain/cramps (on a weekly basis):	
none (0-3 points)	0
mild (4-10 points)	1
moderate (11-17 points)	2
severe (18-21 points)	3
④ General well-being (on a weekly basis):	
good (0-3 points)	0
average (4-10 points)	1
poor (11-17 points)	2
very poor (18-21 points)	3
⑤ Temperature/fever as a result of the ulcerative colitis (°C):	
≤ 38	0
> 38	3
⑥ Extraintestinal manifestations	
none	0
iritis	3
erythema nodosum	3
arthritis	3
⑦ Laboratory findings	
ESR ≤ 50 mm and Haemoglobin (Hb) ≥ 100 g/l	0
ESR > 50 mm but ≤ 100 mm in 1st hour	1
ESR > 100 mm in 1st hour	2
Hb < 100 g/l	4

The values for the calculation of the DAI (① - ④)	Score
① Stool frequency (on a weekly basis):	
normal	0
1-2 stools/day > normal	1
3-4 stools/day > normal	2
> 4 stools/day > normal	3
② Rectal bleeding (on a weekly basis):	
none	0
streaks of blood	1
obvious blood	2
mostly blood	3
③ Mucosal appearance:	
normal	0
mild friability	1
moderate friability	2
exudation, spontaneous bleeding	3
④ Physician's rating of disease activity:	
normal	0
mild	1
moderate	2
severe	3

Table 13 continued.

EI = sum of individual points	Score
Granulation scattering reflected light:	
no	0
yes	2
Vascular pattern:	
normal	0
faded/disturbed	1
completely absent	2
Vulnerability of mucosa:	
none	0
slightly increased (contact bleeding)	2
greatly increased (spontaneous bleeding)	4
Mucosal damage (mucus, fibrin, exudate, erosions, ulcers):	
none	0
slight (< 10 ulcers/10 cm mucosa)	2
pronounced (≥ 10 ulcers/10 cm mucosa)	4

Histology - mucosal inflammation

Evaluation	Score
no ulcerative colitis	0
remission	1
mild activity	2
moderate activity	3
severe activity	4

Evaluator's comment

The choice of CAI as the primary efficacy variable is consistent with that required by the Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis (CHMP/EWP/18463/2006)**Error! Bookmark not defined.**. That is, it reflects the clinical ctivity of the disease and includes a mix of symptoms and signs. Also, it does not include

endoscopy which is not always advisable because of a potential confounding influence and observer variation.

The theshold for the primary endpoint of CAI ≤ 4 at the final visit appears to have been based on its earlier use in published studies. Papers by Rachmilewitz 1989[21] and Rutgeerts 1989[24] were cited in the study protocol as having defined clinical remission as CAI ≤ 4. However, no actual justification was given by Rachmilewitz (on behalf of an international study group) as to why the theshold of 4 was chosen. The guideline requires that the primary endpoint should reflect a normalisation of stool frequency, lack of urgency and absence of blood in the stools. Given the way in which the scores of the individual components of the CAI are calculated (for example, some scores are based on multiple diary entries over the duration of a week), a theshold score of 4 seems reasonable. However, of further note, in the study reported by Rachmilewitz eligibility for enrolment required a baseline CAI of ≥ 6, rather than 4 as in BUF-9/UCA. Thus, the actual magnitude of change required for a clinical response in BUF-9/UCA was lower.

Note: In its response to the first round CER, the sponsor considered endpoint definitions as part of its discussion in support of efficacy of Budenofalk foam (see *List of Questions* below).

Sample size

The calculation of the planned sample sizes was based on the primary efficacy variable, clinical remission which, based on literature data was expected to be 0.55 and a non-inferiority limit of -15% (absolute difference in remission rates). The sponsor had originally chosen an inferiority margin of 20% but this was changed to 15% on the suggestion of the German regulatory authority (BfArM). The narrower non-inferiority margin necessitated an increase in sample size. Consequently, a 4 stage group sequential adaptive design (with sample size adjustments after each planned interim analyses) was used rather than a fixed sample size design because it was felt that the increase of sample size could have been limited with that method.

The first interim analysis was planned to be performed after 2 x 43 ITT evaluable patients finished the trial, the second interim analysis after further 2 x 43 ITT evaluable patients, the third interim analysis after further 2 x 86 ITT evaluable patients and the final analysis after further 2 x 86 ITT evaluable patients had finished the trial. An independent data monitoring committee was established to undertake the group-sequential analyses.

For (one-sided) $\alpha = 0.025$ the critical values for rejection of the null hypothesis were given by 4.049, 2.863, 2.337 and 2.024 for the first, second, third and fourth analysis, respectively. This procedure was noted to have preserved the overall Type I error rate.

Evaluator's comment

The final study report contained no justification for the choice non inferiority margin of 15% other than the fact that the German BfArM had suggested it and no indication was given as to how that particular figure was derived. However, the protocol justified the original choice of a delta of 0.2 by citing recent meta-analyses that showed that placebo remission rates in distal ulcerative colitis were between 0.07 and 0.11 for clinical response.[25, 26] The sponsor reasoned that since the primary endpoint used in this study was clinical remission based on the CAI, a placebo response of not more than 0.15 could be expected but then chose a delta of 0.20. The BfArM presumably required a delta of 0.15 rather than 0.20, based on the same studies. Given

[24] Rutgeerts P. Comparative efficacy of coated, oral 5-aminosalicylic acid (Claversal) and sulphasalazine for maintaining of ulcerative colitis. *Aliment Pharmacol Ther* 1989; 3: 183-91.

[25] Ilnyckyj A, Shanahan F, Anton PA, et al. Quantification of the placebo response in ulcerative colitis. *Gastroenterology* 1997; **112(6)**: 1854-8.

[26] Marshall JK, Irvine EJ. Rectal aminosalicylate therapy for distal ulcerative colitis – a meta-analysis. *Aliment Pharmacol Ther* 1995; **9**: 293-300.

the similarity of the study populations and the definitions of remission in the cited studies to those planned for BUF-9/UCA and the fact that such a difference would be clinically meaningful, the clinical evaluator considers a delta of 0.15 was appropriate.

Note: The sponsor confirmed that the BfArM had required a delta of 0.15 rather than 0.20.

Randomisation and maintenance of blinding

A computerised randomisation procedure was employed, using country-specific randomisation lists generated by the program "Rancode +" (version 3.6) of IDV, Gauting (Germany). Patients were randomised in blocks of four into two treatment groups and two strata within each treatment group (for the sequence of administration of the double-dummy). Randomisation tables were stored in closed, non-transparent envelopes at the trial master file of the sponsor and at the file of the CROs.Emergency envelopes were produced for use in the case of an emergency, however these were all returned unopened at the end of the trial.

Statistical methods

Analyses of the primary and secondary efficacy endpoints were performed on both the PP and ITT populations, with the PP analysis chosen *a priori* as the primary analysis.

Primary efficacy evaluation

Clinical remission was analysed using the Farrington-Manning type non-inferiority χ^2 test for difference of proportions with Mantel-Haenzel stratification for treatment sequence and logistic regression for analysis of covariate effects.

Secondary efficacy evaluation

Change of CAI, number of stools, number of bloody stools and change of DAI were analysed by summary statistics with 95% confidence intervals for the difference in mean changes from baseline. Time to first clinical remission was analysed using survival analysis (median time to remission) and calculation of Hazard ratio with confidence intervals; Cox regression. Clinical improvement based on CAI, clinical remission and improvement based on DAI, endoscopic remission and improvement, histological improvement, therapeutic success and benefit (PGA) were analysed using absolute and relative frequencies, and difference between proportions with confidence intervals. Acceptance and preference endpoints were analysed using absolute and relative frequencies.

Participant flow

A total of 541 patients were randomised (269 to BUF and 272 to EBE); 537 patients were treated (268 with BUF and 269 with EBE) and 482 patients completed the study (239 with BUF and 243 with EBE). One patient in each treatment group was lost to follow-up and 53 (9.9%) patients discontinued treatment prematurely; 28 (10.5%) in the BUF group and 25 (9.3%) in theEBE group. Reasons for discontinuation were similar for the two treatment groups and included lack of efficacy (BUF 12 (4.5%); EBE 11 (4.1%)), lack of co-operation (10 (3.7%) in each group), intolerable adverse events (BUF 5 (1.9%); EBE 1 (<1.0%)), violation of entry criteria (BUF 1 (<1.0%); EBE 2 (<1.0%)) and device malfunction (EBE 1 (<1.0%).

Six patients were excluded from all evaluations; four of these did not receive any medication and two did not have any follow-up data recorded. This gave a safety analysis population of 535 patients (BUF 267; EBE 268).

A further 2 patients (both from the BUF treatment group) certainly did not have ulcerative colitis; the histological diagnoses in these patients were Crohn's disease and collagenous colitis, respectively. This gave an ITT analysis population of 533 (BUF 265; EBE 268).

A total of 209 protocol deviations were recorded in 207 (38%) patients (BUF 124; EBE 83). The most common deviation (51 patients; BUF 32 and EBE 19) was failure to comply with selection criteria, of which most were either insufficient confirmation of the diagnosis (no histology, stool

culture positive or missing) or use of inadequate contraceptive measures. Also, 7 patients older than 70 years of age were included. The inclusion criterion of CAI > 4 was not satisfied by 7 patients (BUF 3; EBE 4)

Not all violations of selection criteria (and indeed other protocol violations) led to exclusion of the patient from the PP analysis. Relevant and irrelevant violations were defined in the statistical plan before breaking the blinding of the trial. The full disposition of patients and assignment to analysis sets are shown in Figures 9 and 10, respectively. Reasons for exclusion were generally similar across the two groups, with the exception of inadequate treatment compliance which was much higher in the BUF group. This was thought to be due to the much more stringent requirement for BUF patients to return their bottles for counting and weighing to give a fairly precise measure of the amount of foam used, whereas for the EBE patients only the number of enemas used could be assessed and not the amount of suspension applied for practical and hygiene reasons. The PP analyses were conducted on data from 449 patients; 210 in the BUF group and 239 in the EBE group.

Figure 9. Participant disposition – Study BUF-9/CDA

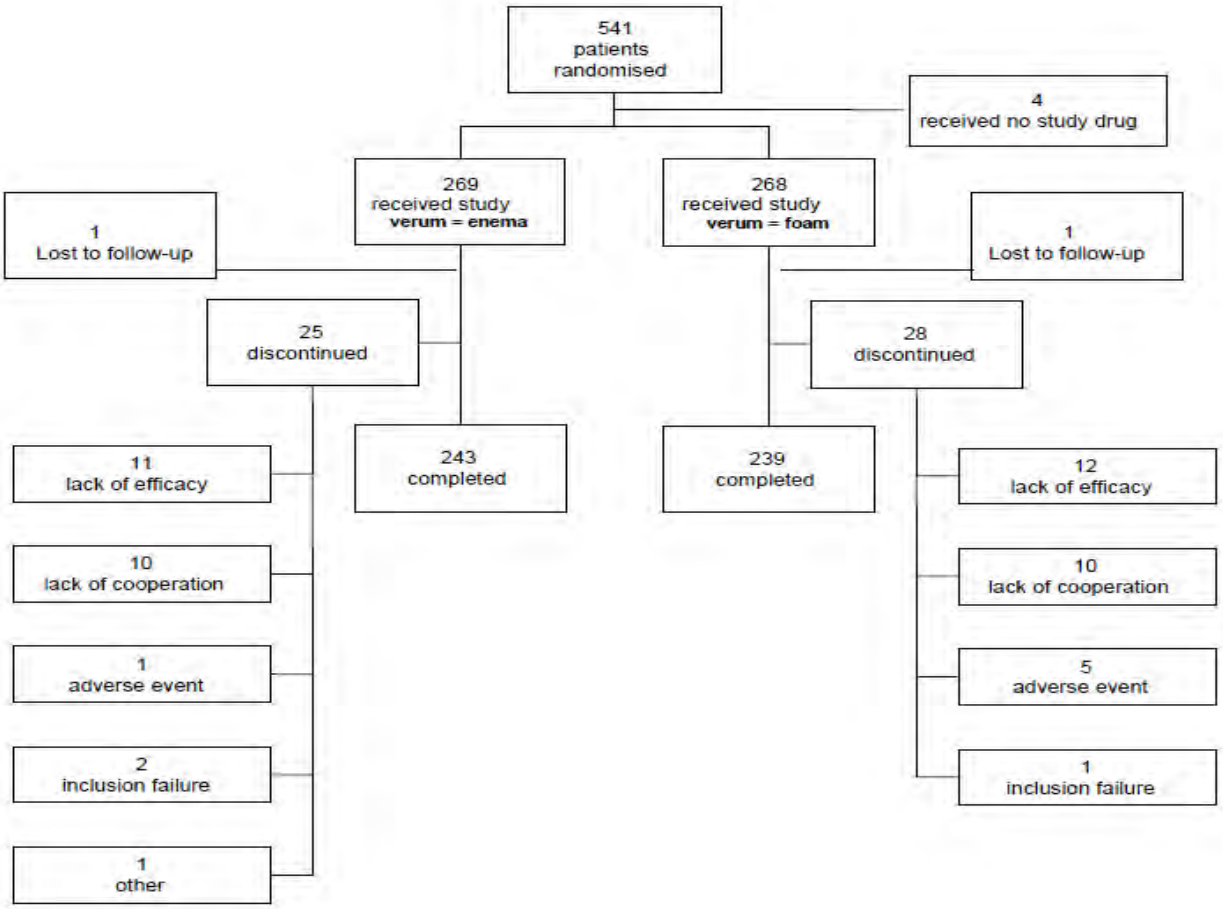
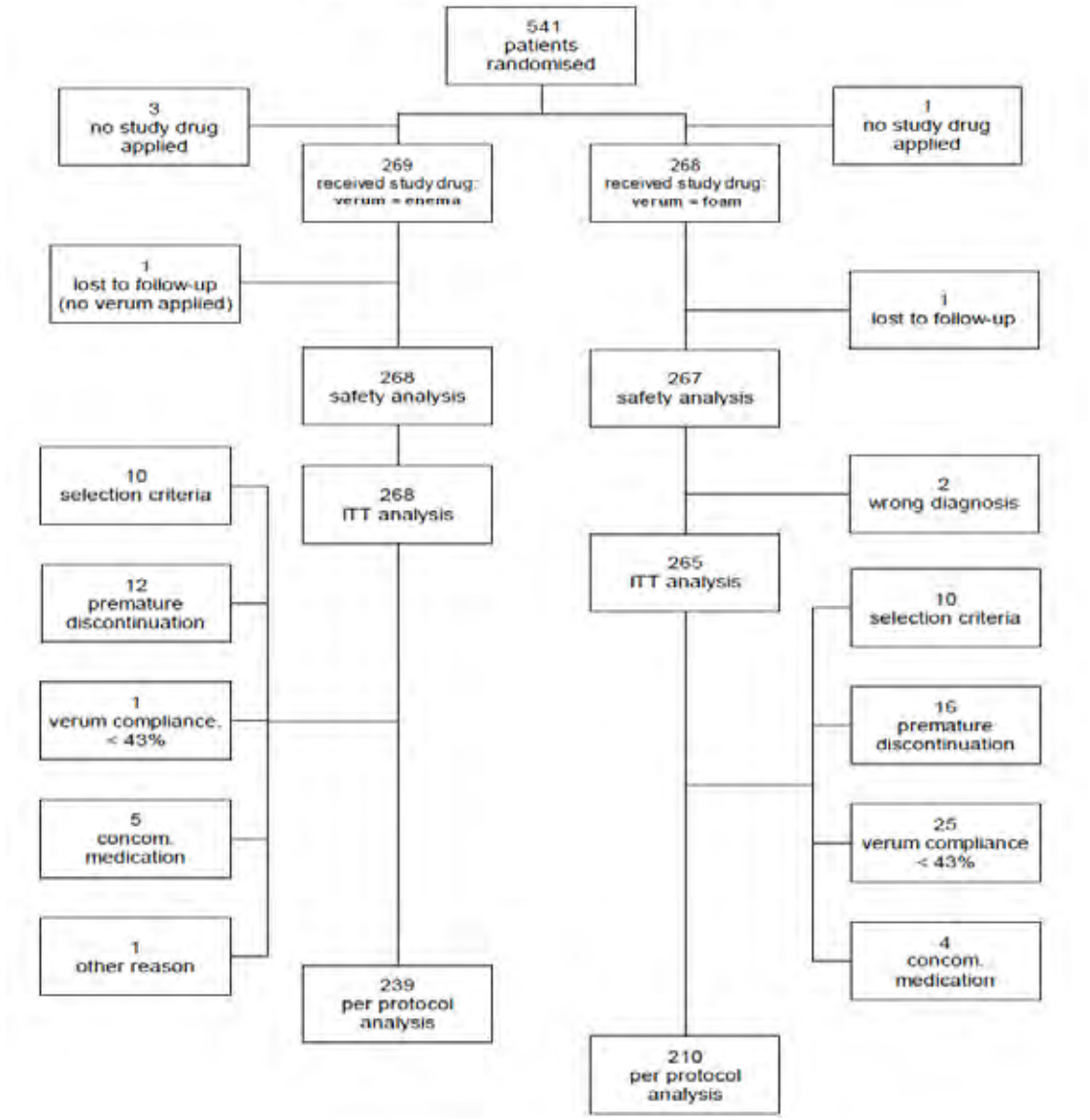


Figure 10. Assignment to analysis sets – Study BUF-9/UCA



Baseline data

Overall, the two treatment groups were very similar with regard to the demographic and disease characteristics at baseline. However, it should be noted that the duration of ulcerative colitis (and, accordingly, the number of previous episodes) was slightly higher in the BUF group, as was the presence of concomitant diseases affecting the cardiovascular, other gastrointestinal and musculoskeletal disease. Also of particular note, there was a difference between the geographical clusters with respect to the baseline covariate of the proportion of patients with a length of inflammation >30 cm, which was considerably higher in the Baltic States (43%) than in the other geographical clusters (such as Germany/ Netherlands 15%; Hungary 23%; Israel 19%). Similar results were obtained for the PP population.

Results for the primary efficacy outcome

Clinical remission (CAI ≤ 4 at the final/ withdrawal examination) was achieved in 60% BUF patients and 66% EBE patients, with a between group (BUF-EBE) difference of -6.2% with 95%CI -14.9% to 3.8%, p=0.02362 (adjusted for randomised treatment sequence) on the PP analysis.

Sensitivity analyses were also performed according to study protocol. An un stratified PP analysis, which ignored treatment sequence, yielded a 95% CI of -14.7 to 4.0% (p=0.02123) consistent with the primary analysis. However, the stratified PP analysis that allocated patients to sequences as treated yielded slightly different results in that the 15% non-inferiority theshold was breached and the p value was greater than 0.025 (95%CI of -15.1% to 3.7%; p=0.02578). In this regard it is noted that 24 patients deviated from the randomised sequence for at least one day (10 patients randomised to sequence "f" and 14 randomised to sequence "e"). The statistical analysis plan required that these patients were assigned to the treatment sequence which they applied on the majority of days. Consequently 2 patients shifted from sequence "f" to "e" and 9 patients shifted from sequence "e" to "f".

The ITT analysis results also yielded 95% confidence intervals that exceeded the non-inferiority margin: the ITT results adjusted for the randomised treatment sequence resulted a between group (BUF-EBE) difference of -8.0% with 95%CI -17% to 0.3% (p = 0.07340), the un-stratified test yielded a 95% CI of -16.8% to 0.5% (p = 0.06691) and the stratified ITT analysis that allocates patients to sequences as treated resulted in a 95% CI of -17.1% to 0.2% (p = 0.07759).

Significant centre effects were not observed. However, there were considerable differences between the geographical clusters. In the PP analysis set, the remission rates in the Baltic States were 72% for budesonide enema and 55% for Budenofalk foam, whereas the rates in the other clusters (Germany/Netherlands, Hungary and Israel) were 61-64% for both treatment groups.

It was also found that remission rates were approximately 10% higher in patients taking foam in the morning and enema in the evening than in patients taking enema in the morning and foam in the evening. This was observed for both treatment groups and for the PP as well as the ITT analysis set. As both treatment groups were equally affected there was no relevant interaction between sequence and treatment, suggesting Budenofalk foam showed better efficacy in the morning and budesonide enema better efficacy in the evening.

Evaluator's comment

Although purely speculative on the part of the clinical evaluator, it is possible that such a difference may be explained by an interaction between the physicochemical characteristics of the two products (stiff viscous foam versus liquid) and the level of physical activity at the different times (for example, recumbence in the evening may predispose to better retention and spread of the liquid enema)

Analysis of clinical remission by baseline covariates is summarised in Table 14. Of particular note, localisation of disease did not have an obvious effect on clinical remission in the logit model, whereas severity of disease at baseline as measured by CAI had a clear influence on remission rates; patients with a low CAI (≤ 8) at baseline achieved clinical remission more frequently than patients with high CAI (p=0.0003). This was higher for the EBE group but only just statistically significant (adjusted odds ratio 1.43; 95%CI: 1.005 to 2.041).

Table 14. Clinical remission by baseline covariates (ITT analysis) - Study BUF-9/UCA

	Number (%) of patients in clinical remission (CAI) at Visit 3 (LOCF)		Adjusted odds ratio* [95%-confidence interval]
	Budenofalk foam	Budesonide enema	
Baseline CAI			1.430 [1.005, 2.041]
<= 8	118/199 (59%)	137/193 (71%)	
> 8	32/66 (49%)	35/74 (47%)	
Localisation			1.404 [0.991, 1.994]
Proctitis	61/105 (58%)	68/99 (69%)	
Proctosigmoiditis	89/160 (56%)	105/169 (62%)	
Duration of disease			1.371 [0.967, 1.949]
<= 5 years	79/135 (59%)	107/159 (67%)	
> 5 years	71/130 (55%)	66/109 (61%)	
Smoking history			1.404 [0.991, 1.995]
non-smoker	101/188 (54%)	126/195 (65%)	
ex-smoker	37/57 (65%)	32/50 (64%)	
smoker	12/20 (60%)	15/23 (65%)	
Extraintestinal manifestations			1.391 [0.980, 1.977]
absent	146/249 (59%)	165/254 (65%)	
present	4/16 (25%)	8/14 (57%)	
Non-response to rectal mesalazine (present episode)			1.398 [0.986, 1.986]
no	134/226 (59%)	149/229 (65%)	
yes	16/39 (41%)	24/39 (62%)	
Non-response to oral mesalazine (present episode)			1.350 [0.950, 1.921]
no	117/198 (59%)	148/218 (68%)	
yes	33/67 (49%)	25/50 (50%)	
Non-response to rectal mesalazine (previous episodes)			1.391 [0.982, 1.975]
no	137/240 (57%)	161/246 (65%)	
yes	13/25 (52%)	12/22 (55%)	
Non-response to oral mesalazine (previous episodes)			1.391 [0.982, 1.975]
no	128/221 (58%)	148/230 (64%)	
yes	22/44 (50%)	25/38 (66%)	

Results for other efficacy outcomes

The analysis of secondary efficacy (ITT) outcomes are summarised in Table 15. The mean change of the CAI was nearly identical between budesonide 2 mg foam and budesonide 2 mg enema (-3.9 versus -4.1), as well as the reduction in the number of bloody stools per week, which is a predominant symptom of distal ulcerative colitis (-14.1 versus -14.4). In addition, the rate of endoscopic remission (EI <4 at final visit (LOCF)) were virtually identical for the two groups on both ITT and PP analyses.

ESR was included as a component of the CAI. Generally the ESR and CRP can be considered indicators of inflammatory activity and are therefore essentially efficacy parameters in this setting. There were no statistically or clinically significant changes in the mean and median levels and interquartile ranges of the ESR or CRP in either budesonide treatment group during the study. Some 31% of patients in the BUF group and 35% in the EBE group had newly occurring or worsening abnormalities in ESR above the ULN. Approximately 26% patients in each group had newly occurring or worsening abnormalities in CRP above the ULN.

Regarding acceptance of the two preparations, 89% of patients reported the foam canister was "easy" to use, whereas only 29 % of patients reported the liquid enema was "easy" to use.

Table 15. Secondary efficacy outcomes (ITT analysis) – Study BUF-9/UCA

		Treatment group		Difference between changes* [CI]
		Budenofalk foam	Budesonide enema	
Change of CAI	mean	-3.7	-3.9	-0.200 [-0.792, 0.391
Change of number of stools per week	mean	-11.6	-12.6	-0.963 [-3.954, 2.029
Change of number of bloody stools per week	mean	-12.9	-13.7	-0.724 [-3.847, 2.401
Change of DAI	mean	-3.5	-3.9	-0.433 [-0.927, 0.061
Time to first clinical remission	median [CI]	9 [7, 12]	7 [5, 10]	**Hazard ratio** 1.109 [0.911, 1.350]
				Difference between proportions* [CI]
Clinical improvement rates (CAI)	n/N_t (%)	211/265 (80%)	223/267 (84%)	-0.039 [-0.105, 0.027
Clinical remission rates (DAI)	n/N_t (%)	134/241 (56%)	158/248 (64%)	-0.081 [-0.168, 0.006
Clinical improvement rates (DAI)	n/N_t (%)	200/241 (83%)	215/247 (87%)	-0.041 [-0.104, 0.023
Endoscopic remission rates	n/N_t (%)	127/243 (52%)	134/248 (54%)	-0.018 [-0.106, 0.071
Endoscopic improvement rates	n/N_t (%)	179/243 (74%)	197/248 (79%)	-0.058 [-0.133, 0.017
Histological improvement rates	n/N_t (%)	117/241 (49%)	134/242 (55%)	-0.068 [-0.157, 0.021
Therapeutic success rates (PGA)	n/N_t (%)	141/263 (54%)	163/267 (61%)	-0.074 [-0.158, 0.010
Therapeutic benefit rates (PGA)	n/N_t (%)	205/263 (78%)	221/267 (83%)	-0.048 [-0.116, 0.019

N_t: group total; CI: 95% confidence interval; * Budenofalk® foam – budesonide enema

Evaluator's comment

There are two main issues with this study. Firstly whether Entocort liquid enema is an appropriate comparator for the Australian setting and secondly whether non-inferiority has been adequately demonstrated.

Is Entocort an appropriate comparator?

As indicated above, Entocort liquid enema is not and has not been registered in Australia. Thus, it is unknown to the TGA if Entocort liquid enemas have an acceptable level of efficacy. Using published literature to establish that Entocort has acceptable efficacy and safety is somewhat difficult because often the comparator used in reported studies is not always clearly identified by a trade name or, if it is, that product was also not registered in Australia. Therefore, the most useful comparison for establishing the efficacy of Entocort liquid enema for the purposes of this evaluation was though comparative studies with a placebo arm. References contained with the current submission were appraised by the clinical evaluator identify placebo-controlled studies for Entocort. Of the 92 references submitted, 11 could not be assessed because they were in German and a translation had not been provided. Of the remaining 81 references, 10 reported the results of comparative efficacy studies involving the use of a budesonide enema that was either identified as Entocort or, where the trade name was not given, noted as having been supplied by AstraDraco. However, of these only 3 assessed the efficacy of Entocort against placebo; Danielsson et al 1992[27]; Hanauer et al 1998[18] and Lindgren et al 1997[20]. Of note, the publication by Lindgren et al 1997 was an abstract and was unevaluable, leaving 2 papers.

[27] Danielsson A, Löfberg R, Persson T, et al. A steroid enema, budesonide, lacking systemic effects for the treatment of distal ulcerative colitis or proctitis. *Scand J Gastroenterol* 1992; 27: 9-12.

The paper by Hanauer et al 1998[18] provides the most useful information in that the quality of the paper was somewhat better that that of Danielsson et al 1992[27] but not without its own deficiencies and the study was conducted in a much larger population and demonstrated consistent outcomes in favour of budesonide 2 mg/100mL od (the dose used in BUC-9/UCA) compared to placebo across a number of clinical and endoscopic endpoints. On this basis, the clinical evaluator was of the opinion that it was reasonable to accept that Entocort liquid enema has a level of efficacy over and above placebo that is clinically significant, such that the comparison in BUC-9/UCA was considered meaningful.

Has non-inferiority of Budenofalk foam enema to Entocort enema been adequately demonstrated in Study BUF-9/UCA?

If one accepts that Entocort is an appropriate comparator, there remains the issue of whether the non-inferiority of Budenofalk foam enema to Entocort enema been adequately demonstrated.

In non-inferiority studies the ITT and PP analyses have equal importance and should lead to similar conclusions to allow for the most robust interpretation of results (TGA-adopted EU guidance[28]). In this particular study the lower bounds of the 95% confidence intervals for the difference in remission rates from the ITT analysis (approximately -17%) were outside the predetermined margin of -15% and were thus not consistent with the PP results. On this basis, the non-inferiority of Budenofalk cannot be considered to have been convincingly demonstrated.

Note: This issue was dealt with at length by the sponsor in its response to the first round evaluation report.

Other efficacy studies

Study BUF-6/UCA

The objectives of this prospective, active controlled, multicentre, randomised, open label, parallel group study were to demonstrate that Budenofalk foam enema (BUF) 2 mg od was equivalent to hydrocortisone acetate foam (HCA) 100 mg od in terms of efficacy during a treatment period of eight weeks in adult outpatients and inpatients with proctitis or proctosigmoiditis and to show that treatment with Budenofalk foam has improved safety and tolerability compared to hydrocortisone acetate foam, based on the lack of systemic side effects. The study was conducted at 38 centres across Germany, Italy and Israel from April 1998 to February 2000.

The main entry criteria for this study were very similar to those for study BUF-9/UCA except that the Disease Activity Index (DAI) was used instead of the CAI (see Table 13 for the scoring system). The primary efficacy parameter was clinical remission at the end of treatment (LOCF) (defined as DAI ≤ 3). A range of secondary efficacy parameters were derived. Most of these were either based around changes in the DAI from baseline or the results of endoscopic analyses which assessed mucosal appearance score at baseline and changes from baseline at visits at Days 28 and 56. Bowel biopsies were taken and examined to derive the Histology Index (HI) for each of thee regions (rectum, sigmoid, descending colon) and consequently changes in the HI from baseline. The Patient's Global Impression (PGI) was also determined at each visit and end of treatment.

Results

A total of 248 patients received study medication; 120 patients received BUF 2 mg foam and l28 patients received HCA 100 mg foam. These patients were included in the safety and the ITT analyses. Seventy three (29 %) patients discontinued treatment during the study.

[28] CPMP/EWP/482/99. Points to Consider on Switching between Superiority and Non-inferiority.

Discontuniations were mostly due to lack of efficacy (39 patients). Other reasons for discontinuation included lack of co-operation (10 patients), intolerable adverse events (10 patients) and failure to satisfy the entry criteria (2 patients).

Thirty-two (27 %) patients treated with BUF 2 mg foam and 37 (29 %) patients treated with HCA 100 mg foam were excluded from the PP analysis because of major protocol violations, mostly due to non-compliance with study medication and use of non-permitted prior or concomitant medication, leaving a total PP population of 179 patients; 88 patients in the BUF group and 91 patients in the HCA group.

Both the ITT and PP populations were well balanced at baseline with respect to demographic characteristics. Most disease characteristics were also balanced in the ITT population (such as disease location, method of diagnosis, extra-intestinal manifestations, first episode of disease and time since start of current episode). However, of note, patients receiving Budenofalk had a shorter mean time since first diagnosis; a longer mean duration of episodes and shorter mean time between episodes; and much higher use of rectal 5-ASA for the current episode at study entry (58% versus 35%) than those receiving HCA.

The primary and selected secondary endpoints are summarised in Table 16. Clinical remission was achieved in a similar proportion of patients in both treatment groups at Day 56; BUF 55% versus HCA 51% (Difference in proportions: 4%; 95%CI: -10.6 to 18.6%) on PP analysis and BUF 53% versus HCA 52% (Difference in proportions: 0.16%; 95%CI: -12.3 to 12.6%) on ITT analysis.

Table 16. Primary and selected secondary endpoint results – Study BUF-6/UCA. Table continued across two pages.

	PP		ITT	
	BUF	HCA	BUF	HCA
Primary endpoint				
Clinical remission rate at day 56 with 'not recorded' data treated as lack of remission	48/88 (55%)	46/91 (51%)	63/120 (53%)	67/128 (52%)
Difference in proportion vs. HCA	4.0%		0.16%	
95% CI	-10.6 – 18.6%		-12.3 – 12.6%	
Clinical remission rate at day 56 with 'not recorded' data excluded	48/75 (64.0%)	46/73 (63.0%)	63/104 (61%)	67/106 (63%)
Difference in proportion vs. HCA	0.99%		-2.63%	
95% CI	-14.5 – 16.5%		-15.8 – 10.5%	
Secondary endpoints				
Clinical remission rate at day 28	38/88 (38%)	32/91 (35%)	46/120 (38%)	44/128 (34%)
DAI				

	PP		ITT	
	BUF	HCA	BUF	HCA
Baseline*	7.1 ± 1.88	7.0 ± 1.95	7.2 ± 1.85	7.0 ± 2.01
Change from baseline at Day 28*	-3.2 ± 2.43	-2.6 ± 2.88	-3.0 ± 2.49	-2.6 ± 2.80
Change from baseline at Day 56 (LOCF)*	-3.6 ± 2.87	-2.9 ± 3.35	-3.5 ± 3.01	-3.1 ± 3.26
Difference in least squares mean vs. HCA at day 56 [95%CI]	-0.6 [-1.7 – 0.4]		-0.3 [-1.2 – 0.5]	
p value	0.203		0.427	
Therapeutic benefit (↓ DAI ≥ 1 from baseline)				
At day 28	63/73 (86%)	56/72 (78%)	85/101 (84%)	80/103 (78%)
At day 56 (LOCF)	60/75 (80%)	56/73 (77%)	82/104 (79%)	84/106 (79%)
Time to clinical remission# (days)				
Median [95%CI], p value (vs. HCA)	8 [5–14], 0.72	7 [4 – 11]	7 [5–12], 0.40	9 [6 – 15]
Histologic Index				
Baseline*	3.4 ± 1.07	3.5 ± 1.11	3.4 ± 1.05	3.4 ± 1.07
Day 28*	2.6 ± 1.12	2.9 ± 1.17	2.7 ± 1.15	2.9 ± 1.22
Day 56 (LOCF)*	2.7 ± 1.27	2.6 ± 1.18	2.6 ± 1.20	2.6 ± 1.19
Stool count/week				
Baseline*	31 ± 18.8	30 ± 25.4	31 ± 19.4	30 ± 22.7
At day 28*	18 ± 12.9	19 ± 13.6	19 ± 13.9	20 ± 13.2
At day 56 (LOCF)*	19 ± 17.1	22 ± 21.1	19 ± 17.5	22 ± 19.2
Ratio of Day 56 (LOCF) to baseline				

	PP		ITT	
	BUF	HCA	BUF	HCA
Least squares geometric mean	0.60	0.74	0.59	0.74
p value for ratio to baseline vs. HCA	0.015		0.024	

*=mean ± SD, #=remission defined as≤ 3 stools/day, all blood free

Results for the secondary outcomes were consistent in that improvement in these outcomes were comparable between both treatment groups, including proportions of patients with therapeutic benefit at Days 28 and 56, decreases in DAI score and histologic index and time to clinical remission (defined as no more than 3 daily bowel movements without blood in these stools). Patients receiving BUF had a statistically significantly higher reduction in stool count/week from baseline at Day 56 than those receiving HCA (decrease of 12 stools per week versus 8 stools per week).

Evaluator's comment

The clinical remission rate in the Budenofalk group was numerically higher than that for the hydrocortisone acetate group and this was supported by similar and consistent results for the secondary efficacy parameters. However, in the strictest sense this study failed to show equivalence because the two sided 95%CI interval for the difference in proportions of patients achieving remission did not lie fully within the predetermined range of ± 10% (that is, both boundaries within ± 10%) for either the PP or ITT analyses. The 95%CI for the PP analysis was -10.6% to 18.6% and the 95%CI for the ITT analysis was -12.3% to 12.6%.

Furthermore, the evaluator found the information presented in the study report and protocol to be inconsistent and at times confusing. The protocol very clearly identified the study as an equivalence study both in terms of the objectives of the study and in the description of the considerations undertaken with respect to the sample size calculations. These aspects were restated in the study report. However, in the study report the null hypothesis for the statistical analysis of the primary endpoint was cast in terms of there being an inferiority of more than 10% in the clinical remission rate, with no mention of equivalence at all. Equivalence trials are not the same as non-inferiority trials. If the intention was to analyse the results as a non-inferiority trial, the requirement would have been for the two sided 95% CI to lie entirely above (to the right of) -10%. Once again this was not achieved in either analysis, although the close proximity of the lower bound of the PP analysis (-10.6%) to the predetermined margin (-10%) is noted. In this regard, it must be remembered that in equivalence and non-inferiority studies the ITT and PP analyses have equal importance and they should lead to similar conclusions to allow for the most robust interpretation of results. The lower bound of the 95%CI from the ITT analysis (-12.3%) was outside the predetermined inferiority/equivalence margin. These sorts of considerations are covered at length in the TGA-adopted EU guidance document.[28]

What is of particular importance in equivalence or non-inferiority trials is the need for a high level of compliance with the protocol such that any deviations from inclusion criteria, intended treatment regimen and the precision of taking measurements tend to make a conclusion of no difference or no inferiority more likely. In this particular trial there were a considerable number of major protocol violations. In addition, the primary efficacy endpoint of clinical remission was on the DAI which is a sum of scores of stool frequency, rectal bleeding pattern, mucosal appearance on endoscopy and the physician's rating of disease activity. Each component of the DAI has a degree of subjectivity (some much more than others) which can be a major source of bias in an unblinded study. Furthermore, most of the secondary efficacy parameters were also based on subjective assessments by either the physician or the patient (such as mucosal appearance at each visit, Patient's Global Impression at each follow-up visit). Only the central

pathologist who performed the histological examinations of biopsy material for determination of the HI was blinded to treatment. However, that endpoint would not be entirely devoid of bias either because the endoscopy and choice of sites for biopsy were done by the study investigator who was not blinded to treatment.

See also additional comments regarding choice of comparator above.

Note: This issue was dealt with at length by the sponsor in its response to the first round evaluation report.

Study BUF-5/UCA. Dose finding study for Budenofalk budesonide foam enema in patients with active distal ulcerative colitis

This Phase IIb study was a prospective, placebo controlled, multicentre, randomised, double blind, parallel group trial conducted at 11 centres in Russia and the Ukraine to investigate the efficacy and safety of two doses of budesonide foam (2 mg od or 2 mg bd) compared to placebo in patients with mild to moderate active proctitis or proctosigmoiditis. The study was conducted from August 1997 to July 1998.

Adult patients aged 18 to 70 years with a diagnosis of mild to moderate proctitis or proctosigmoiditis and a Clinical Activity Index (CAI) >4 and ≤ 12, and an endoscopic index ≥ 4 were eligible for study entry. Key exclusion criteria were infectious bowel disease, disease proximal to the sigmoid colon, newly occurring or acute colitis with symptoms present for < 2 weeks, a current requirement for systemic corticosteroids or immunosuppressants or previous receipt of glucocorticosteroids by any route within 1 month of the study or immunosuppressants within 3 months of the study.

Patients received either placebo, budesonide 2 mg daily or budesonide 4 mg daily (2 mg bd) for a period of 6 weeks. Blinding of patients and study personnel was maintained by providing patients with two cans that were identical except for colour coding to signify whether it was a morning or evening dose. Patients randomised to budesonide 2 mg received their active dose in the evening, whilst the budesonide 4 mg group received active medication in the morning and evening.

The primary efficacy endpoint was clinical remission, defined as a CAI score ≤ 4 and a reduction in CAI relative to baseline of at least 2 points. The statistical significance of treatment differences in the proportion of patients at Day 42 with clinical remission was analysed using Cochan-Mantel-Haenszel chi-square test stratified by centre and 95% confidence intervals for the odds of achieving clinical remission for the two budesonide doses compared to placebo were also calculated. A range of secondary efficacy variables were also examined including but not limited to clinical remission at each visit, change from baseline in CAI , change from baseline in the DAI, time to first clinical remission and endoscopic remission at each visit. The ITT population was the primary population for both efficacy and safety analyses and efficacy endpoints were also analysed for the PP population.

Results

A total 223 patients were enrolled and randomised to receive placebo (n=76), budesonide 2 mg (n=71) or budesonide 4 mg (n=76). One patient was randomised but did not receive any study treatment, leaving an ITT population of 222 patients: M:F 92 (41%): 130 (59%); mean (± SD) age 42 ± 12.4 yrs [range 18-70]) and mean (± SD) CAI 7.9 ± 1.9 [range 4-10]. Of these, 179 (81%) patients had proctosigmoiditis and 43 (19%) patients had ulcerative proctitis.

The 3 treatment groups were well balanced at baseline with respect to age, gender and most disease characteristics. The most notable differences between the groups were that patients in the budesonide 4 mg group had a longer time since first onset of symptoms of disease compared to patients in the placebo and budesonide 2 mg groups (median of 69.1 months compared with 43.8 and 47.6 months, respectively) and patients in the placebo group had a shorter mean interval between episodes of active disease (38.9 weeks versus 63 and 51.6 weeks for the

interval between episodes of active disease (38.9 weeks versus 63 and 51.6 weeks for the budesonide 2 mg and 4 mg groups, respectively). All but 2 patients (both in the placebo group) had their ulcerative colitis diagnosed on endoscopy. Between 28 and 36% of patients, depending on treatment group, had also had the diagnosis confirmed histologically at baseline.

The primary and selected secondary endpoints are summarised in Table 17. Clinical remission at the end of treatment was achieved in 61% patients in the placebo group, 56% patients in the Budenofalk 2 mg group, and 62% patients in the Budenofalk 4 mg group. Neither Budenofalk group was statistically significantly different to the placebo group with respect to the primary endpoint or any of the secondary endpoints, including the CAI, DAI, endoscopy index and remission, histological index and improvement. Similar results were found for both the ITT and PP populations and for sub-analyses of clinical remission by site of disease (proctitis, proctosigmoiditis) and disease severity (mild (4<CAI≤8) and moderate (8<CAI≤12)). Of particular note, the placebo response (61%) was much higher than the expected spontaneous remission rate.

The study report contained a detailed discussion of possible contributory factors including incorrect diagnosis of patients, trial medication error, centre effects, non compliance with banned concomitant medication, study population characteristics and the primary endpoint definition, which were all discounted. A retrospective analysis revealed that approximately 50% patients were hospitalised at baseline or during the trial and received intensified medical care. This was thought by the sponsor to have possibly influenced the activity of disease, for most patients with mild to moderate ulcerative colitis would be treated as outpatients in Western countries.

Table 17. Primary and selected secondary efficacy endpoints – Study BUF-5/UCA. Table continued across three pages.

	Placebo n=76	BUD 2mg n=70	BUD 4mg n=76
Primary efficacy endpoint			
Clinical remission	46 (61%)	39 (56%)	47 (62%)
Odds ratio vs. placebo		0.80	1.05
95%CI		0.40 – 1.59	0.50 – 2.19
p value		0.519	0.898
Secondary efficacy endpoints			
Pts with clinical remission by visit			
Day 14	21 (28%)	19 (27%)	21 (28%)
Day 28	20 (26%)	16 (23%)	21 (28%)
Day 42	13 (17%)	9 (13%)	11 (14%)
Any visit	54 (71%)	44 (63%)	53 (70%)
p value vs. placebo (Wilcoxon test)		0.750	0.906

	Placebo n=76	BUD 2mg n=70	BUD 4mg n=76
Clinical activity index			
Visit 1 (Baseline)			
n	76	70	76
Mean ± SD	7.7 ± 1.5	7.5 ± 1.67	7.4 ± 1.97
Median	8.0	7.0	7.0
Range	5.0 – 12.0	5.0 – 12.0	5.0 – 12.0
Visit 2			
n	75	70	76
Mean ± SD	5.8 ± 3.1	5.6 ± 2.66	5.5 ± 2.95
Median	6.0	6.0	5.5
Range	0 – 18.0	0 – 14.0	0 – 12.0
Visit 3			
n	72	67	74
Mean ± SD	4.5 ± 2.96	4.5 ± 2.98	4.0 ± 3.03
Median	4.0	5.0	4.0
Range	0 – 12.0	0 – 12.0	0 – 13.0
Visit 4			
n	68	62	71
Mean ± SD	3.7 ± 3.24	3.5 ± 3.31	2.8 ± 2.64
Median	3.0	2.0	2.0
Range	0 – 11.0	0 – 13.0	0 – 10.0
Visit 4 (LOCF) % change from baseline			
n	76	70	76
Mean ± SD	-3.2 ± 3.81	-3.5 ± 3.47	-4.1 ± 3.14
95% CI for mean	-4.1 to -2.4	-4.3 to -2.6	-4.8 to -3.4
Median	-4.0	-4.0	-4.0

	Placebo n=76	BUD 2mg n=70	BUD 4mg n=76
Range	-11.0 - +11.0	-11.0 - +7.0	-11.0 - +5.0
Diff from placebo (least squares mean)		-0.3	-1.0
95% CI		-1.4 to 0.8	-2.1 to 0.1
p value		0.600	0.065
Endoscopic remission (% pts)			
Day 42	29/68 (43%)	29/62 (47%)	37/71 (52%)
Day 42 (LOCF)	29/73 (40%)	29/67 (43%)	37/75 (49%)
p value (Mantel-Haenszel test)		0.773	0.307
Histological improvement			
Day 42	37/67 (55%)	39/62 (63%)	44/70 (63%)
Day 42 (LOCF)	38/71 (54%)	41/68 (60%)	45/74 (61%)
Odds ratio for remission vs. placebo		1.27	1.36
95% CI		0.65 – 2.48	0.70 – 2.65
p value		0.477	0.363

Evaluator's comment

This was a generally well designed dose response study as evidenced by the use of randomisation, employment of a placebo control group and parallel active groups, blinding, *a priori* sample size calculations (with minimum sample sizes achieved for both the ITT and PP populations) and appropriate statistical analytical methods. The diagnosis of ulcerative colitis was also appropriately based on a combination of patient's symptoms (diarrhoea, bloody stools) and case history, endoscopy, histology and microbiology (exclusion of infections) and disease activity was classified according to the Clinical Activity Index.

The failure to demonstrate statistically significant differences between the Budenofalk and placebo in any of the efficacy endpoints can be attributed to the much higher than expected placebo response rate of 61%. (Note: the *a priori* sample size calculations were based on detecting a 25% difference between the expected placebo response rate of up to 30% and a Budenofalk response rate of 55%). The reason for the higher than expected placebo response was not completely elucidated and this was acknowledged by the sponsor. The sponsor postulated that it is likely that the high hospitalisation rate and resultant intensive medical care increased response rates. However, the sponsor did not provide a breakdown of hospitalisation by treatment group. This is important, for if the proportions of hospitalisations were similar

across the three groups, it would not explain why the placebo response would be higher without the Budenofalk response rate having been similarly affected. Also of note, the observed rates for the Budenofalk groups were similar to those found with budesonide liquid enema in published studies, suggesting the Budenofalk groups were unaffected but this doesn't exclude the possibility that the response to budesonide delivered as a foam enema is intrinsically lower than when delivered as a liquid enema (due to differences in formulation and physicochemical characteristics), which the intensive medical treatment may have counterbalanced.

Another consideration, as noted earlier, is that the batch of Budenofalk foam enema used in this study was outside the lower release specification (RS) for budesonide assay (93.3% versus the RS range 95 – 105%) and sorbic acid content (83.5% versus RS range 90 – 110%).

A final observation by the clinical evaluator was that the justification for doses chosen to elucidate the dose response relationship for budesonide in Study BUF-5/UCA included reference to a company study cited as: Falk Pharma GmbH, Data on File: Efficacy and safety of Budenofalk foam (2 mg per puff) and Betamethasone 5 mg enema – An open, randomised, multicentre, controlled clinical trial. Biometrical report 1996.

In that study of 22 patients it was purportedly shown that budesonide 2 mg enema administered twice a day for two weeks had shown an average reduction in the CAI of 48%. However, this particular study has not been included in this submission and has not been included in the overall summaries of efficacy or safety.

Note: The issue of higher than expected placebo response in Study BUF-5/UCA s has been covered in detail by the sponsor as part of its response to the first round evaluation report. With regard to the 22 patient study mentioned above, the sponsor indicated that the study (BUF-3/UCA) was conducted using a budesonide foam product with a substantially different volume (double volume).

Analyses performed across trials (Pooled Analyses and Meta-Analyses)

Nil analyses were performed.

Evaluator's conclusions on clinical efficacy for active distal ulcerative colitis, proctitis and proctosigmoiditis

The sponsor has submitted three efficacy studies for Budenofalk foam enema:

- a large Phase III non-inferiority study (BUF-9/UCA), in which the efficacy of budesonide 2 mg foam (Budenofalk) o.d. in inducing remission was compared to the budesonide 2 mg enema (Entocort) od in 541 patients with active distal UC;
- a smaller Phase III equivalence study (BUF-6/UCA), in which the efficacy of budesonide 2 mg foam (Budenofalk) od in inducing remission was compared to a hydrocortisone acetate 100 mg foam formulation (Colifoam) od in 251 patients with active distal UC; and
- a Phase IIb dose-finding study (BUF-5/UCA), in which the efficacy of 2 mg od and 2 mg bd of budesonide foam (Budenofalk) in inducing remission was compared to placebo in 233 patients with mild to moderately active proctitis or proctosigmoiditis.

The key efficacy results from these studies are summarised in Table 18 which also provides a comparison of the durations of treatment and definitions for clinical remission. Notwithstanding the differences in definitions of remission and durations of treatment, the clinical remission rates were quite similar across the three studies. There were also common features across the studies with respect to analyses of remission rates by baseline covariates:

- milder episodes of ulcerative colitis were associated with higher remission rates than moderate episodes;

- localisation of disease to the rectum was associated with higher remission rates than disease also involving the sigmoid colon; and
- a longer duration of disease (more than 5 years) was associated with lower remission rates.

Of particular note, the placebo remission rate in Study BUF-5/UCA was similar to that for the active treatments in the other studies. Study BUF-5/UCA was essentially a failed dose finding study in which neither Budenofalk dose was statistically significantly different to the placebo group with respect to the primary endpoint or any of the secondary endpoints. Therefore, it does not contribute significantly to the demonstration of efficacy. This leaves the two Phase III studies for consideration. Of these studies, the sponsor's *Clinical Overview* stated:

> "The efficacy of budesonide 2 mg (Budenofalk) foam o.d. in the treatment of distal active UC was convincingly demonstrated in two active-controlled, multicentre, randomised, parallel-group Phase III clinical trials, which can be regarded as pivotal studies…… Budesonide 2 mg (Budenofalk) foam showed good efficacy in patients with distal UC and proved to be not inferior to an approved and marketed budesonide 2 mg enema formulation (Entocort), and also therapeutically equivalent to an approved and marketed hydrocortisone acetate 100 mg foam (Colifoam) formulation."

This statement highlights several of the main issues that need to be resolved in deciding if Budenofalk foam has acceptable efficacy. Firstly, contrary to the statement made in the sponsor's *Clinical Overview*, neither of the active comparators used in the Phase III studies are marketed in Australia. The sponsor's *Clinical Overview* was written specifically for European submission and the statements regarding marketing status do not reflect the situation in Australia. Entocort liquid enema is not entered in the Australian Register of Therapeutic Goods (ARTG). Also, although a Colifoam product is entered in the ARTG, there is no indication the product used in Study BUF-6/UCA is the same as that marketed here (and, in fact, there is evidence to suggest it is not).

Secondly, the sponsor has considered Study BUF-6/UCA to be pivotal. The clinical evaluator disagreed with that conclusion because the study was open label and therefore potentially subject to observer and measurement bias. This is a particularly important consideration because the primary efficacy endpoint was based on changes in a composite score derived from an assessment of a number of subjective components. Similarly, many of the secondary endpoints were based on subjective assessments. It is important to note that the TGA-adopted EU *Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis*[29] states that Phase III studies in ulcerative colitis should, amongst other requirements be double-blinded. Importantly, the sponsor's *Clinical Overview* document did not contain any reconciliation of the data submitted with the TGA's regulatory requirements.

[29] CHMP/EWP/18463/2006. http://www.tga.gov.au/pdf/euguide/ewp1846306en.pdf

Table 18. Key results from submitted efficacy studies. Table continued across two pages.

	BUF-9/UCA Results at 4 weeks (Clinical remission: CAI ≤ 4 at 4 wks)		BUF-6/UCA Results at 8 weeks (Clinical remission: DAI ≤ 3 at 8 wks)		BUF-5/UCA Results at 6 weeks (Clinical remission: CAI ≤ 4 and ↓ in CAI of ≥ 2 at 6 wks)		
	BUF 2mg	EBE 2mg	BUF 2mg	HCA 100mg	BUF 2mg	BUF 4mg	Placebo
Clinical remission							
ITT population	57%	65%	53%	52%	56%	62%	61%
PP population	60%	66%	55%	51%	53%	65%	63%
Covariate analyses for clinical remission (ITT)							
Disease severity							
CAI ≤ 8	59%	71%			63%	67%	66%
CAI > 8	49%	47%			29%	44%	41%
DAI ≤ 6			68%	63%			
DAI > 6			41%	44%			
Disease location							
Proctitis	58%	69%	55%	67%	60%	69%	75%
Proctosigmoiditis	56%	62%	51%	45%	55%	60%	58%
Disease duration							
≤ 5 yrs	59%	67%	57%	53%			
> 5 yrs	55%	61%	46%	52%			
Non-response to rectal mesalazine for current episode	41%	62%	52%	37%			

Table 18 continued.

Secondary outcomes using LOCF (ITT)							
Mean change in CAI	-3.7	-3.9			-3.5	-4.1	-3.2
Mean change in DAI	-3.5	-3.9	-3.5	-3.1	-2.9	-3.2	-2.9

Secondary outcomes using LOCF (ITT)							
Mean change in stools/wk	-11.6	-12.6					
Time (days) to remission (<3 blood free stools/day)	9	7	7	9			
Endoscopic remission (EI<4)	52%	54%			43%	49%	40%
Mean change in EI	-3.5	-3.7			-2.6	-2.8	-2.2

The evaluator accepted the use of Entocort as a comparator in Study BUF-9/UCA based on an evaluation of two published papers. One paper (Hanauer et al 1998[18]) was considered to have demonstrated consistent outcomes in favour of budesonide 2 mg/100mL od (the dose used in BUC-9/UCA) compared to placebo across a number of clinical and endoscopic endpoints.

However, a further consideration must be whether it is sufficient for the sponsor to have submitted a single pivotal study. A relevant guide in this situation is the TGA-adopted EU document titled *Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal Study*[30]. This document indicates that where confirmatory evidence is provided by a single pivotal study, the study would need to be *exceptionally compelling*, with special attention paid to internal and external validity, the clinical relevance of the findings and *the degree of statistical significance* (the italicising is the clinical evaluator's emphasis). In Study BUF-9/UCA, although the primary efficacy analysis (PP population) demonstrated that the 95% CI lay entirely to the right of -15%, the findings were not particularly compelling because the conclusions of the ITT analyses and the stratified PP analysis were not consistent with those of the primary non stratified PP analysis. For non-inferiority studies, ITT and PP analyses have equal importance and should lead to similar conclusions to allow for the most robust interpretation of results. In this regard the following was noted:

- the 95% CI for the stratified (sequences as treated) PP analysis was -15.1% to 3.7% and therefore breached in the non-inferiority theshold; and
- all the 95% confidence intervals for the ITT analyses breached the non-inferiority margin:
  - -16.8% to 0.5% for the non-stratified ITT analysis;
  - -17% to 0.3% for the ITT analysis adjusted for the randomised treatment sequence;
  - -17.1% to 0.2% for the stratified (sequences as treated) ITT analysis.

Moreover, the *Points to Consider* document mentioned above highlights that when the aim of the single pivotal study is to demonstrate non-inferiority, the lower 95% confidence bound should be well away from the inferiority margin. In Study BUF-9/UCA this was not achieved with any analysis, including the primary (non stratified PP) analysis, where the lower bound of the 95% CI for the difference in proportions was -14.9%.

The *Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis* requires that for studies evaluating induction treatment only, a follow-up period off-treatment is mandatory. This was not done in any of the submitted studies.

The final overriding consideration is that none of the studies were conducted using a formulation that contained propylene glycol as a constituent of the rectal foam (which is the

[30] CPMP/EWP/2330/99. http://www.tga.gov.au/pdf/euguide/ewp233099en.pdf

formulation proposed for Australia). Even small differences in the composition (including non active substances) of locally applied, locally acting products may influence their physicochemical properties. The stiffness and stability of the foam may have been altered which, in turn, may have affected the extent of penetration and efficacy of the active compound. Consequently, therapeutic equivalence has to be shown (as per the Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents, pp 193 – 198 of The Rules Governing Medicinal Products in the European Union 1998 (3C – 3CC12a)**Error! ookmark not defined.**). There were no data demonstrating the therapeutic equivalence of the pre and post 2006 formulations and no justification as to why such an assessment was not necessary.

Thus, in the opinion of the clinical evaluator, insufficient data have been submitted to demonstrate the acceptable efficacy of the Budenofalk foam enema.

Note: The issues of, firstly, whether Study BUF-6/UCA is a pivotal study and, consequently, whether the efficacy of Budenofalk rectal foam has been established were discussed at length in the sponsor's response to the first round evaluation report (see *List of Questions* below for the clinical evaluator's assessment and acceptance of the response and the clinical evaluator's final assessment of the benefits of the product).

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy Study – BUF-9/UCA

In the pivotal efficacy Study BUF-9/UCA the following safety data were collected:

- General adverse events (AEs) were assessed at Visits 2 (Day 14 ± 4) and 3 (final visit/Day 28 ± 7). AEs were either reported spontaneously by the patient, observed by the study investigator or elicited by the non directive question "Has your health worsened since you last saw me?". The date and time of onset, description, intensity, duration and outcome, aetiology, relationship of the adverse event to study drug and action taken were recorded in the Case Report Form (CRF). AEs were categorised as serious and non serious using the standard International conference on harmonisation (ICH) definition.
- Treatment emergent AEs were summarised by body system and by the number and frequency of patients who experienced at least one adverse event within that body system. Similar summary tables were produced for the number and frequency of patients with possibly drug related adverse events, serious adverse events and withdrawals due to adverse events. The incidence of adverse events was summarised by treatment group and compared using appropriate statistical analyses.
- Laboratory tests, comprising standard haematology and biochemistry parameters (but not bilirubin) and urinalysis, were performed at Visits 1 (baseline/Day 0), 2 (Day 14 ± 4) and 3 (final visit/Day 28 ± 7). The number of patients with low, normal or high laboratory values; the percentage change from baseline; and clinically significant laboratory values and newly occurring/worsening laboratory abnormalities were also summarised for each parameter by treatment group.
- Laboratory tests of particular interest were serum cortisol levels, which were measured at baseline and the final visit at Dday 28. Absolute serum cortisol levels, changes from baseline and the proportion of patients with cortisol deteriorations (either above or below normal range) were measured to assess the degree of adrenal and pituitary suppression.

- Vital signs (blood pressure, pulse and body weight) were tabulated at each visit and the change from baseline was summarised.
- A global assessment of tolerability by patient and study investigator at the final/withdrawal examination.

Pivotal studies that assessed safety as the sole primary outcome

There were no studies that assessed safety as the sole primary outcome.

Dose response and non pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- Study BUF-6/UCA provided data on reported adverse events at Visits 2 (Day 14 ± 3), 3 (Day 28 ± 7) and 4 (final visit/Day 56 ± 7), changes in laboratory parameters (standard haematology and biochemistry) at each visit, vital signs at each visit, and a global assessment of tolerability by patient and investigator at Visits 2, 3 and 4. Laboratory tests of particular interest were serum cortisol levels (measured at each visit) and the serum bone markers osteocalcin and bone-specific alkaline phosphatase (measured at Visits 1, 3 and 4).
- The dose response Study BUF-5/UCA provided data on reported adverse events at Visits 2 (Day 14 ± 3), 3 (Day 28 ± 7) and 4 (final visit/Day 42 ± 7), changes in laboratory parameters (standard haematology, biochemistry and immunology (erythrocyte sedimentation rate (ESR)) at each visit, vital signs at each visit and a global assessment of tolerability by patient and investigator at Visits 2, 3 and 4. Laboratory tests of particular interest were serum cortisol, aldosterone and CRP levels (measured at Visits 1 (baseline/Day 0) and 4).

Evaluator's comment

Although the dose and duration of treatment with BUF varied across these two studies, the studies each included a group treated with the recommended daily dose of BUF and adverse events were elicited in a fashion similar to that used in the pivotal efficacy study. Also, the safety populations in these studies were effectively the ITT populations. Consequently, the AEs and vital signs data are presented collectively under the subheading Other studies below. The AEs from these studies are contrasted with the results from the pivotal study in a tabular format to summarise the safety according to dose and duration of treatment.

The range of standard haematology and biochemistry parameters measured on study were alsosimilar. Data were presented in terms of the proportions of patients with clinically significant abnormal laboratory results but insufficient information was provided in the reports to be able to validly assess the outcomes. There were no definitions or criteria for determining what was clinically significant (such as >upper limit of normal (ULN), > 2-3 times ULN, <lower limit of normals (LLN)) and the results were presented without explanation so one did not know whether the change was bidirectional (if it incorporated values both above and below the normal range, in which case it is conceivable that two groups could have the same proportion yet one could have exclusively increased results and the other exclusively decreased results), whether it was unidirectional (which would be more relevant if one was looking for changes secondary to a specific pharmacological action or disease activity) or whether it was required to be associated with clinical manifestations. This information is critical to interpreting a statement such as that given in Study BUF-5/UCA that "there were no statistically significant differences between either of the budesonide groups and placebo in the proportion of patients with clinically significant laboratory abnormalities or in the incidence of these laboratory abnormalities".

Furthermore, in Study BUF-5/UCA the protocol stated that the incidence of clinically significant laboratory values would be summarised and analysed statistically for "selected laboratory

parameters" but did not specify these parameters a priori. Of note, the study report did not present any results by way of an analysis of clinically significant abnormalities in standard biochemistry results.

In view of these issues, the clinical evaluator found it necessary to review the supporting listings of Individual Patient Data (IPD) to get a sense of what these results meant for Study BUF-5/UCA. The IPD base for the tabulation in the study report was referenced as Listing 31 and Listing 32. Perusal of the listing for patients who received placebo in Listing 31 identified additional serious concerns about the identification of laboratory abnormalities for:

- Centre 01: all ALT values were denoted as high even when they were below or within the normal range;
- Centre 02: all creatinine values were denoted as low even when they were above or within the normal range;
- Centre 03: all ALT, γGT and alkaline phosphatase values were denoted as high even when they were below or within the normal range;
- Centre 04: all ALT and alkaline phosphatase values were denoted as high even when they were below or within the normal range;
- Centres 05, 06, 07 and 08: all creatinine levels were denoted as low even when they were above or within the normal range;
- Additionally for Centre 06: all haematocrit values were denoted as high even when they were below or within the normal range;
- Additionally for Centre 08: all haemoglobin (Hb) levels were denoted as high even when they were below or within the normal range and, furthermore, one patient was noted to have had Hb levels of 136 g/l, 13.3 g/l and 13.7 g/l at successive visit, suggestive of data entry error/confusion of scientific units for the parameter; and
- Centre 09: all alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (γGT) values were denoted as high, irrespective of whether they were below or within the normal range.

A complete review of the IPD Listing for all other patients within the study is beyond the scope of this evaluation and additional errors in data entry and the denoting of abnormal results cannot be ruled out.

The IPD in Study BUF-6/UCA were also checked in light of the above findings and the denoting of abnormalities was found to be acceptable. However, in Study BUF-6/UCA what was immediately apparent on perusal of the tabulation of changes in haematology and biochemistry parameters from baseline in the study report was that the ranges of values for the changes from baseline did not make sense and could not be reconciled with the mean and median scores. Every range at every visit for every parameter in hydrocortisone group had negative minimum and maximum bounds, whilst every range at every visit for every parameter in the BUF group had positive minimum and maximum bounds. Furthermore, the values of the mean and median change did not sit within any of the ranges presented, irrespective of the treatment group or visit number. This suggests that the ranges for the two groups have been mixed up, that is, the ranges presented for hydrocortisone group are likely to be the lower bound of the range for each group, whilst the ranges presented for BUF are probably the upper bounds of the ranges for each treatment group. It appears the table was taken directly from the output of the statistical package.

The summary statistics and changes from baseline for vital signs and serum cortisol, osteocalcin and bAP levels were presented in separate analyses in Study BUF-6/UCA and no errors in the tabulation of results were found by the clinical evaluator. In that study samples were assayed for these parameters at a central laboratory. Similarly, the cortisol, aldosterone and electrolyte

assays for Sstudy BUF-5/UCA were performed centrally and the denoting of change from baseline appeared error free. Thus, the pharmacodynamic laboratory parameters (that is, cortisol, aldosterone and electrolytes) were accepted by the clinical evaluator and presented in this CER (see Pharmacodynamics above).

Note: The laboratory data from Studies BUF-5/UCA and BUF-6/UCA have been re-analysed and addenda to the sponsor's study reports submitted as part of the sponsor's response to the first round evaluation questions (see List of Questions below)

Clinical pharmacology studies

Reported adverse events and standard haematology and biochemistry were assessed in the clinical pharmacology Studies BUF-7/BIO and BUF-4/BIO. In Sstudy BUF-7/BIO systemic pharmacodynamic effects were also assessed by collecting full 24 h profiles of serum cortisol levels and blood lymphocyte and granulocyte counts, whilst in Study BUF-4/BIO vital signs were also assessed at each visit. Study BUF-7/BIO was undertaken in 18 in healthy volunteers, whilst Study BUF-4/BIO was conducted in 12 patients with active distal ulcerative colitis.

Pivotal studies that assessed safety as a primary outcome

No studies submitted.

Patient exposure

Patient exposure to Budenofalk rectal foam is summarised in Tables 19 and 20, below. The overall clinical development program involved 1035 individuals of whom 1017 were patients with documented distal ulcerative colitis and 18 participants were healthy volunteers.

A total of 563 individuals received at least one dose of Budenofalk foam rectally. Of these 563 individuals, 487 with ulcerative colitis received the recommended daily dose of 2 mg od, 267 received treatment for 4 weeks, 70 received treatment for 6 weeks and 120 received treatment for 8 weeks. The remaining 30 individuals were from the clinical pharmacology program received either a single nominal 2 mg dose and/or received 2 mg for 4 days only.

The draft Product Information proposes that the duration of treatment be no more than 8 weeks (and usually 6 to 8 weeks), with the actual duration of use being determined by the physician. Safety data have been presented for 190 patients who received the recommended dose for what according to the draft PI is the usual duration of treatment, with data from a further 267 patients who received the recommended dose for a shorter period.

Adverse events

All adverse events (irrespective of relationship to study treatment)

Pivotal Study – BUF-9/UCA

In the pivotal study, a total of 143 AEs were reported by 86/267 (32%) patients in the BUF group and 133 AEs were reported by 87/268 (33%) patients in the EBE group. Most AEs occurred in the gastrointestinal tract (BUF 11.6%; EBE 9.3%) and nervous system (BUF 10.9%; EBE 11.9%). A summary of AEs by system organ class (SOC) is presented in Table 21a. AEs with an incidence of >1.5% (> 4 patients) in either treatment group were headache (BUF 10.1%; EBE 10.8%), abdominal pain not otherwise specified (BUF 3.0%; EBE 2.2%), ulcerative colitis aggravated (BUF 1.5%; EBE 3.7%); nausea (BUF 3.0%; EBE 0.7%), dyspepsia (BUF 1.9%; EBE 1.5%) and anxiety (BUF 0.4%; EBE 1.9%).

Gastrointestinal disturbances such as nausea and dyspepsia would be considered potentially steroid-associated adverse drug reactions (ADRs). Other events that are consistent with known

corticosteroid side effects (but not necessarily causally related in this study) were: 3 reports of hypertension in the BUF group (2 of which were considered by the study investigator to be ADRs) and 1 report of weight increased in each treatment group (both cases considered to be ADRs).

Almost all the AEs reported in each treatment group were of mild or moderate intensity. Severe AEs occurred in 1 BUF patient (report of dyspepsia) and 5 EBE patients (3 reports of ulcerative colitis aggravated; 1 report each of renal colic and CVA).

Table 19. Exposure to Budenofalk foam (BUF) and comparators in clinical studies

Study type/ Indication	Controlled studies				UC studies	Total Bud
	Bud foam enema	Pbo	Bud liquid enema Entocort	Hydro-cortisone acetate foam	Bud foam	
Clinical pharmacology						
Healthy volunteers					18	18
Ulcerative colitis pts					12	12
Distal ulcerative colitis						
Pivotal	267		268			535
Supporting study	120			128		248
Dose-finding study	146	76				222
TOTAL	533	76	268	128	30	1035

Bud=Budesonide; Pbo=Placebo; UC=Uncontrolled

Table 20. Exposure to rectal Budenofalk in clinical studies according to dose and duration

Study type/ Indication	Dose range				Duration of treatment				
	0mg	2 mg od	2 mg bd	Any dose	≤ 5 days	4 wks	6 wks	8 wks	Any dur'n
Clinical pharmacology									
Healthy volunteers		18*	18*	18*	18				18
Ulcerative colitis pts		12		12	12				12
Distal ulcerative colitis									
Placebo-	76	70	76	146			146*		146**

Study type/ Indication	Dose range				Duration of treatment				
	0mg	2 mg od	2 mg bd	Any dose	≤ 5 days	4 wks	6 wks	8 wks	Any dur'n
controlled							*		
Active-controlled		387		387		267		120	387
Uncontrolled				0					0
TOTAL	76	487*	94*	563*	30	267	146**	120	563

* Healthy volunteers received budesonide 2 mg on Day 1 then 2 mg b.d.on days 2 to 5, inclusive (BUF-7/BIO).

** 70 at 2 mg od and 76 at 4 mg daily

Other studies

The results for studies BUF-6 and -5/UCA are shown individually in Tables 21b and 22 respectively. Table 23 shows those AEs with an incidence of 3% in at least one of the BUF arms in any of the supporting efficacy studies and presents the corresponding results from the pivotal study. The incidence of AEs observed with the recommended single daily dose of 2 mg Budenofalk over 8 weeks in Study BUF-6/UCA (30%) was comparable to that seen with the 2 mg daily dose over 4 weeks in the pivotal study. The rates of AE reporting in the dose finding study (BUF-5/UCA) were approximately half that of the Phase III studies and no dose response relationship was elicited.

Of particular note:

- headache was consistently reported as one of the most common AEs, however, it was more frequently reported in the pivotal study than the supporting studies;
- application site reactions were reported at between 3 and 7% in the dose finding study, whereas it was rarely reported, if at all, in the other studies;
- infections were only reported with longer term use (8 weeks) at the recommended daily dose or with higher dose (4 mg daily) over 6 weeks; and
- nausea, dyspepsia and gastrointestinal disturbance were reported at variable rates across the studies and, although they could be reasonably anticipated with corticosteroid use (as they are known side effects), none were considered by the investigators to be causally related in these studies. Also, reports of fever, increased ESR and abdominal pain were reported at variable rates across the studies and most likely reflect the underlying disease. (Note: in the pivotal study a number of cases of aggravation of ulcerative colitis were recorded as AEs).

Table 21a. Summary of Adverse Events by SOC. Study BUF9/UC

System Organ Classes	Number (%) of patients with AEs	
	Budenofalk foam (n=267)	Budesonide enema (n=268)
Gastrointestinal disorders	31 (11.6%)	25 (9.3%)
Nervous system disorders	29 (10.9%)	32 (11.9%)
Infections and infestations	12 (4.5%)	11 (4.1%)
Investigations	11 (4.1%)	9 (3.4%)
General disorders and administration site conditions	6 (2.2%)	4 (1.5%)
Musculoskeletal and connective tissue disorders	6 (2.2%)	7 (2.6%)
Respiratory, thoracic and mediastinal disorders	6 (2.2%)	0
Cardiac disorders	3 (1.1%)	0
Vascular disorders	3 (1.1%)	0
Psychiatric disorders	2 (0.7%)	8 (3.0%)
Renal and urinary disorders	2 (0.7%)	4 (1.5%)
Blood and lymphatic system disorders	1 (0.4%)	1 (0.4%)
Skin and subcutaneous tissue disorders	1 (0.4%)	1 (0.4%)
Immune system disorders	1 (0.4%)	0
Eye disorders	0	1 (0.4%)
Injury, poisoning and procedural complications	0	1 (0.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.4%)

Table 21b. Summary of Adverse Events by System Organ Class. Study BUF-6/UCA

Adverse Event by Body System	Number (%) of patients experiencing treatment-emergent AE	
	Budesonide 2 mg N = 120	Hydrocortisone acetate 100 mg N = 128
Body as a whole		
any event	17 (14%)	24 (19%)
abdominal pain	7 (6%)	9 (7%)
headache	4 (3%)	6 (5%)
infection	4 (3%)	2 (2%)
asthenia	2 (2%)	2 (2%)
flu syndrome	2 (2%)	2 (2%)
back pain	1 (<1%)	2 (2%)
fever	1 (<1%)	2 (2%)
Digestive system		
any event	15 (13%)	14 (11%)
diarrhoea	5 (4%)	2 (2%)
gastrointestinal disorder	3 (3%)	3 (2%)
rectal disorder	2 (2%)	3 (2%)
rectal haemorrhage	2 (2%)	1 (<1%)
nausea	0	2 (2%)
Haemic and lymphatic system		
any event	4 (3%)	6 (5%)
sedimentation rate increased	3 (3%)	4 (3%)
leukocytosis	2 (2%)	1 (<1%)
Metabolic and nutritional		
any event	2 (2%)	5 (4%)
alkaline phosphatase increased	0	2 (2%)
peripheral oedema	0	2 (2%)
Musculoskeletal system		
any event	1 (<1%)	7 (5%)
myalgia	1 (<1%)	2 (2%)
arthralgia	0	2 (2%)
Respiratory system		
any event	3 (3%)	7 (5%)
bronchitis	0	4 (3%)
cough increased	1 (<1%)	2 (2%)
Skin and appendages		
any event	5 (4%)	4 (3%)
acne	2 (2%)	1 (<1%)
Urogenital system		
any event	2 (2%)	2 (2%)
urinary tract infection	2 (2%)	0

Table 22. Summary of Adverse Events by System Organ Class - Study BUF-5/UCA

	placebo (n=76) N(%)	budesonide 2 mg (n=70) N(%)	budesonide 4 mg (n=76) N(%)
Body as a whole	5(7%)	7(10%)	7(9%)
Headache	4(5%)	4(6%)	4(5%)
Digestive system	4(5%)	4(6%)	4(5%)
Nausea	1(1%)	3(4%)	1(1%)
Vomiting	2(3%)	2(3%)	0
Skin + appendages	5(7%)	2(3%)	5(7%)
Application site reaction	4(5%)	2(3%)	5(7%)
Respiratory system	0	2(3%)	2(3%)
Cardiovascular system	3(4%)	0	0
Musculoskeletal system	1(1%)	2(3%)	0
Nervous system	3(4%)	0	0
Urogenital system	0	1(1%)	2(3%)
Special senses	0	1(1%)	0

Also of note, in the BUF group in Study BUF-6/UCA there were 2 reports of acne, 1 report of increased appetite, 1 report of hypertension and 1 report of new diabetes mellitus Type II. Such events that are consistent with known corticosteroid side effects and, with the exception of the case of diabetes mellitus, all were considered to have a causal relationship with the study drug.

Evaluator's comment

The potential for bias with attribution of causality and severity ratings to AEs in the open label setting was noted.

The case of new onset diabetes mellitus was diagnosed and recorded as an AE in a 61 year old patient 43 days after the commencement of BUF. The patient's glucose level was normal at baseline (71 mg/dL; normal range (NR): 70 – 100 mg/dL) and thereafter steadily rose over the course of the study (81 mg/dL at Day 14; 102 mg/dL at Day 28 and 116 mg/dL at Day 56). These were the only biochemical abnormalities detected for this patient whilst on study. Glycated hemoglobin (HBA_{1c}) was not measured. It is of note that the patient had a BMI of 28.9 at baseline (weight 100 kg; height 186cm) and was known to be hypertensive. There was no record of previous medications for this patient so it assumed there were no other medications that could have contributed to the condition. Notwithstanding the possible contribution of the patient's weight to the development of diabetes, given the strong temporal relationship, a co contribution from the budesonide cannot be excluded and under these circumstances it would have been reasonable to assign a possible causality rating as per the criteria set out in the study protocol.

Table 23. Adverse events with an incidence of 3% in at least one of the BUF arms in any of the supporting efficacy studies, contrasted with rates from the pivotal study

	Pivotal study		Supporting studies			
	4 weeks (BUF-9/UCA)		6 weeks (BUF-5/UCA)			8 weeks (BUF-6/UCA)
	BUF 2mg od, n=267	EBE 2mg od, n=268	Placebo, n=76	BUF 2mg od, n=70	BUF 4mg od, n=76	BUF 2mg od, n=120
Any AE	32%	33%	16%	16%	18%	30%
Withdrawal due to AE	4.1%	2.6%	0	0	0	3%
Most common AEs						
Headache	10.1%	10.8%	5%	6%	5%	3%
Abdominal pain	3.0%	2.2%	0	1%	1%	6%
Application site reaction	0.4%	0.4%	5%	3%	7%	0
Infection	0	0	0	0	1%	3%
Diarrhoea	0.7%	0	0	0	0	4%
Nausea	3.0%	7.0%	1%	4%	1%	0
GIT disorder	0	0	5%	6%	5%	3%
↑ ESR	0	0	0	0	0	3%
Fever	0	0	0	3%	1%	<1%

	Pivotal study 4 weeks (BUF-9/UCA)		Supporting studies 6 weeks (BUF-5/UCA)			8 weeks (BUF-6/UCA)
	BUF 2mg od, n=267	EBE 2mg od, n=268	Placebo, n=76	BUF 2mg od, n=70	BUF 4mg od, n=76	BUF 2mg od, n=120
Back pain	1.1%	1.5%	0	3%	0	<1%
Vomiting	0.4%	0	3%	3%	0	0
Dyspepsia	1.9%	1.5%	0	0	3%	0
Ulcerative colitis aggravated	1.5%	3.7%	0	0	0	0
Deaths	0	0	0	0	0	0
SAEs	<1%	1.5%	1%	0	0	<1%
ADRs	10.1%	7.1%	5%	4%	7%	6.7%
Application site reaction	0.4%	0.4%	5%	3%	7%	0
Headache	1.5%	1.1%	0	0	0	<1%
Abdominal pain	1.5%	<1%	0	0	0	0
Nausea	1.5%	<1%	0	1%	0	0
↑ ALT	1.1%	0	0	0	0	0

Treatment - related adverse events (adverse drug reactions)

Pivotal Study – BUF-9/UCA

A total of 27 (10.1%) patients in the BUF group and 19 (7.1%) in the EBE group experienced at least one ADR. The most common ADRs were headache (BUF n=4; EBE n=3), abdominal pain (BUF 4; EBE 2), nausea (BUF 4; EBE 1), dyspepsia (BUF 2; EBE 2), ALT increased (BUF 3) and γGT increased (BUF 2; EBE 1). Other ADRs occurring in 2 or fewer patients in total (both groups) included aspartate aminotransferase (AST) increased, alkaline phosphatase increased, amylase increased, rash, flatulence, diarrhoea, hypertension, back pain and application site pain.

Other studies

The overall ADR rates were comparable across the supporting studies, with no dose response observed in the dose finding study. Of note, the ADR rate for BUF over 4 weeks in the pivotal study (10%) was higher than that observed for BUF at the recommended daily dose over 6 and 8 weeks, largely due to the higher rate of headache, abdominal pain, nausea and increased ALT. In addition to the application site reactions, one report of nausea was considered to be an ADR in the dose finding study.

Deaths and other serious adverse events

Pivotal studies

There were no deaths during the course of the pivotal study.

A total of 7 serious adverse events (so classified because the patient was hospitalised) occurred in 6 patients: 2 (0.75%) in the BUF group and 4 (1.5%) in the EBE group. Vignettes were provided for each of the serious AEs.

In the BUF group one patient was hospitalised with aggravated ulcerative colitis 14 days after the study drug was discontinued because of lack of efficacy (which was after only 4 days of treatment). This particular patient had a baseline Carbonic Anhydrase Inhibitor (CAI) of 12 and had required oral prednisone prior to study entry. The other patient with a serious AE in the BUF group required hospitalisation for unstable angina 10 days after completion of the study drug. Two patients in the EBE group (with CAIs of 7 and 8 at baseline) had their budesonide enema discontinued because of inefficacy and were later hospitalised with aggravation of their ulcerative colitis. A third patient in this group was hospitalised with a cerebrovascular accident (CVA) (stroke) and pneumonia 6 days after commencing study drug. The fourth EBE patient required a “nepholith operation” for renal colic which started 7 days after commencement of study drug. This patient made a good recovery and recommenced study drug 4 days post op and went on to achieve clinical remission. None of the serious AEs were considered causally related to study drug, which was considered reasonable.

Other studies

No deaths were reported in any of the supporting studies.

Only one serious adverse event was recorded for BUF in the supporting studies. In Study BUF-6/UCA a 42 year old patient developed persistent diarrhoea 5 days after commencing treatment. The event persisted for 33 days and led to the withdrawal of the patient from the study. The event subsequently resolved without sequelae. (Note: the serious AE in the placebo group in Study BUF-5/UCA was a report of ventricular fibrillation in a 42 year old).

Discontinuation due to Adverse Events

Pivotal studies

In the pivotal study 11 (4.1%) patients in the BUF group and 7 (2.6%) in the EBE group discontinued the study due to AEs. Several discontinuations in each group were either due to aggravated ulcerative colitis (3 in BUF group and 2 in the EBE group) or due to an AE that in all likelihood represented a deterioration in the disease itself (in the EBE group 1 patient had rectal haemorrhage and another had haemorrhagic diarrhoea). Other AEs leading to discontinuation in the BUF group were abdominal pain not otherwise specified (2 patients) and upper abdominal pain, nausea, dyspepsia, flatulence/frequent bowel movements, unstable angina and abnormal liver transaminases (all 1 patient each). In the EBE group additional discontinuations were due to back pain/headache and CVA/pneumonia.

Other studies

There were few discontinuations due to AEs in the BUF groups across the supporting studies. There were no discontinuations because of AEs in the dose finding study. In Study BUF-6/UCA, 4 (3%) patients receiving Budenofalk foam enema discontinued primarily because of intolerable AEs (which was consistent with the rates in the pivotal study). Two of these patients had diarrhoea and one had worsening of colitis, all of which were not considered causally related to budesonide. The fourth discontinuation was a 40 year old patient with a urinary tract infection (UTI) that was considered to be possibly related to the study medication. One additional patient discontinued because of laboratory abnormalities (leucocytosis and increased ESR).

Laboratory tests

Liver function

Pivotal study – BUF-9/UCA

AST, ALT, γGT, alkaline phosphatase and total protein concentrations were monitored thoughout the pivotal study. There were no statistically or clinically significant changes in the mean and median levels and interquartile ranges of any of these parameters in either budesonide treatment group. Serum bilirubin levels were not monitored.

Newly occurring or worsening levels above the normal range were observed as follows: AST (BUF 5.3%; EBE 4.2%); ALT (BUF 8%; EBE 7.2%); γGT (BUF 10.7%; EBE 8.7%); alkaline phosphatase (BUF 3.0%; EBE 3.8%). Insufficient information prevented assessment of whether any of these abnormalities were suggestive of liver injury, for example patients with ALT, AST >2-3 x ULN or the patterns of liver function test (LFT) abnormalities. Total protein level deteriorations were BUF 5.7% and EBE 4.2% for deteriorations above ULN and BUF 4.2% and EBE 4.2% for deteriorations below LLN.

Abnormalities in LFTs that were considered to be causally related to study medication (that is, ADRs) were: ↑ALT - BUF n=3; ↑AST - BUF n=2; ↑γGT - BUF n=2, EBE n=1; ↑alkaline phosphatase BUF n=1; and "abnormal liver function test" – EBE n=1. Two patients in the BUF group discontinued from the study as a result of mildly elevated AST and ALT levels. One of these patients subsequently recovered, whilst the other had not shown signs of recovery by the end of the study.

Other studies

See evaluator's comments under *Safety* below.

Kidney function

Pivotal Study – BUF-9/UCA

Creatinine and urea levels were monitored thoughout the pivotal study. There were no statistically or clinically significant changes in the mean and median levels and interquartile ranges of either of these parameters in either budesonide treatment group.

Newly occurring or worsening levels above the normal range during treatment were observed as follows: creatinine BUF 20 (7.6%), EBE 14 (5.3%); urea BUF 16 (6.1%), EBE 6 (3.1%). Only one ADR was reported for the System Organ Class (SOC) Renal and Urinary Disorders, that of a case of proteinuria with EBE.

Other studies

See evaluator's comments under *Safety* below.

Other clinical chemistry

Pivotal Study – BUF-9/UCA

Serum sodium and potassium were monitored during the study. There were no statistically or clinically significant changes in the mean and median levels and interquartile ranges of either of these parameters in either budesonide treatment group. Serum chloride levels were not monitored.

Newly occurring or worsening hyponatraemia was observed in 4.9% BUF patients and 3.4% EBE patients, whilst hypernatraemia was observed in 1.1% BUF patients and 2.3% EBE patients. Newly occurring or worsening hypokalaemia was observed in 4.9% patients in the BUF group compared to 3.4% in the EBE group. Hyperkalaemia was observed in 7.6% BUF patients and 3.4% EBE patients. None of the abnormalities in serum sodium or potassium levels were considered to be ADRs.

Other studies

See evaluator's comments under *Safety* below.

Haematology

Pivotal study – BUF-9/UCA

Haemoglobin concentration, haematocrit, and erythocyte, leucocyte and platelet counts were monitored during the study. There were no clinically significant changes in the mean and median levels and interquartile ranges of any of these parameters in either budesonide treatment group. White cell differential counts were not assessed.

The incidence of newly occurring or worsening levels below the normal range for haemoglobin, haematocrit and erythocyte levels were much more common (by an approximately an order of magnitude) than newly occurring or worsening levels above the normal range for both budesonide groups (approximately 20% decreased and 2% increased for each parameter). Conversely, newly occurring or worsening levels above the normal range were much more common than levels below the normal range for leucocyte and platelet counts (approximately 10-15% increased versus 2% decreased). All of the abnormalities in haematological parameters (with the exception of 1 case each of decreased haematocrit and decreased haemoglobin) were considered by the study investigator to be related to the underlying ulcerative colitis.

Other studies

See evaluator's comments under *Safety* below.

Amylase

Pivotal Sstudy – BUF-9/UCA

There were no statistically or clinically significant changes in the mean and median levels and interquartile ranges of serum amylase concentrations in either budesonide treatment group during the study. Newly occurring or worsening levels above the normal range were observed in 16 (6.1%) patients in the BUF group and 19 (7.2%) patients in the EBE group. One case of increased amylase was recorded as an ADR in the BUF group but no other details were given.

Other studies

This parameter was not assessed in the supporting studies.

Electrocardiograph (ECG)

ECG was not performed in any of the studies.

Vital signs

Pivotal Study – BUF-9/UCA

Blood pressure, pulse and body weight remained virtually unchanged thoughout the study. AEs of note were 3 reports of hypertension in the BUF group (2 of which were considered to be ADRs), 2 cardiac rhythm disorders (sinus tachycardia and tachycardia not otherwise specified)in the BUF group (nether report considered to be causally related to study drug) and reports of weight increased in 1 patient in the BUF group and 1 in the EBE group (both causally related).

Other studies

Blood pressure, pulse, temperature and body weight in each treatment group remained virtually unchanged thoughout both supporting studies. Only 1 BUF patient (from Study BUF-6/UCA) developed hypertension, which was considered to be causally related to study medication. No disturbances of cardiac rhythm or weight gain were observed in any patients receiving BUF. In Study BUF-6/UCA there was one case of hypertension and 2 arrhythmias (extrasystole and ventricular fibrillation) in the placebo group.

Postmarketing experience

Line listings of all adverse events reported from market launch to15 November 2009 indicate that only 4 AEs have been reported for the Budenofalk foam enema:

1. 2 reports of allergic exanthema; one assigned a possible causal relationship (positive de-challenge) and the other a certain causal relationship (positive de-challenge and re-challenge, occurring 1 and 11 days, respectively after commencement of treatment for ulcerative colitis);
2. a case of maculopapular exanthema (of possible causality, with negative rechallenge) occurring 2 weeks after commencing the foam enema for the treatment pouchitis; and
3. a case of pancreatitis with positive de-challenge (assigned a probable causality and also considered to be a serious event), occurring 3 days after commencement of treatment.

Evaluator's comment

The submission contained a single Periodic Safety Update Report (PSUR) dated 2003 (pre dating the international launch of the foam enema). Once again this indicates the sponsor submitted an out-of-date submission for the foam enema.

Note: Additional PSUR documents were submitted as part of the sponsor's response to the first round evaluation questions.

Specific safety issues of regulatory importance

Liver toxicity

Nil issues identified.

Haematological toxicity

Nil issues identified.

Serious skin reactions

Nil issues identified.

Cardiovascular safety

Nil issues identified.

Unwanted immunological events

Nil issues identified.

Other safety issues

Safety in special populations

There were no separate studies in the elderly or patients with hepatic impairment.

Evaluator's comment

Whilst separate studies in the elderly are not specifically required by the TGA adopted guideline *Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis*, it is recommended that the clinical development program should ensure there are adequate numbers of elderly patients included in the trials. A pooled safety analysis was not performed and there has been no presentation within the sponsor's *Summary of Clinical Safety* by way of breakdown of patients according to age (such as age ≤60 versus age >60yrs) across the studies. Only summary statistics have been presented in the individual study reports and therefore it was not possible to determine the proportion of elderly patients in the clinical development programe.

Regarding studies of patients with hepatic impairment, it is known that budesonide is metabolised by CYP3A4 in the liver and in fact, first pass metabolism is relied upon to limit its systemic exposure. Metabolism of budesonide may be decreased and systemic exposure to budesonide may be increased in patients with impaired hepatic function. This issue is addressed further in the application to register Budenofalk (budesonide 3 mg) oral capsules for the treatment of mild to moderate active Crohn's Disease.

Safety related to drug-drug interactions and other interactions

No information generated.

Evaluator's overall conclusions on clinical safety

There was a generally consistent approach to the monitoring of safety across the studies submitted with the application. Safety was evaluated in all studies by way of reported adverse events, changes in laboratory parameters (standard haematology and biochemistry) and vital signs. In addition, systemic pharmacodynamic effects were assessed though monitoring of serum cortisol levels (Studies BUF-7/BIO, BUF-5/UCA, BUF-6/UCA and BUF-9/UCA), bone markers (BUF-6/UCA), and the global assessment of tolerability by patient and investigator (Phase IIb and III studies).

Overall, there were no unexpected adverse events or reactions in the context of the known safety profile of glucocorticosteroids. There were no withdrawal or rebound phenomena recorded in any of the studies. Clinically relevant adrenal suppression was not been observed in patients treated for up to 8 weeks. However, it is important to note that only 120 patients were exposed to Budenofalk foam for the recommended maximum duration of treatment of 8 weeks.

The rates of AEs and ADRs observed with Budenofalk were generally consistent with those of its active comparators in the Phase III studies but none of the studies assessed safety as a primary endpoint. Key findings across the submitted studies were:

- headache was consistently reported as one of the most common AEs, however, it was more frequently reported in the pivotal study than the supporting studies;
- infections were only reported with longer term use (8 weeks) at the recommended daily dose or with higher dose (4 mg daily) over 6 weeks; and
- nausea, dyspepsia and gastrointestinal disturbance were reported at variable rates across the studies and, although they could be reasonably anticipated with corticosteroid use (as they are known side effects), none were considered by the investigators to be causally related in these studies. Also, reports of fever, increased ESR and abdominal pain were reported at variable rates across the studies and most likely reflect the underlying disease. (Note: in the pivotal study a number of cases of aggravation of ulcerative colitis were recorded as AEs).

Of note, application site reactions were reported at between 3 and 7% in the dose finding study, whereas it was rarely reported, if at all, in the other studies. The nature of the application site reactions (such as pain, local excoriation, local bleeding) were not described in any detail. No explanation was offered by the sponsor as to why this was almost exclusively reported in the dose finding study and the only apparent difference from the other studies was that there was a high rate of hospitalisation of patients which may have influenced the recording and reporting of such reactions.

A pooled safety analysis was not performed and consequently there has been no breakdown of safety and tolerability according to age (such as age <60 versus age >60 yrs) across the studies. Also, only summary statistics have been presented in the individual study reports, so it is not possible to get an indication of the proportion of elderly patients in the clinical development program.

The main concerns with the safety data submitted were:

- the apparent errors in the tabulation and analysis of IPD laboratory data (Studies BUF-5 and -6/UCA) and in the outputs of the statistical analysis package (Study BUF-6/UCA);
- the absence of safety data (and particularly local tolerability of the propellants and foam constituents) with repeated courses of Budenofalk foam over time (that is, the treatment of repeated flares of active disease with the formulation intended for supply in Australia); and
- the absence of post marketing experience data for Budenofalk foam enema, despite its international birthday having been in 2006.

Note: The concerns regarding the safety data was addressed by the sponsor in its response to TGA questions (see *List of Questions*for the clinical evaluator's assessment and acceptance of the response and the clinical evaluator's final assessment of the safety of the product below).

List of questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "List of Questions" to the sponsor is generated.

Clinical questions

General

- Sorbic acid was used as an antimicrobial preservative thoughout the pharmaceutical and clinical development program. It was removed from the formulation and replaced by propylene glycol post approval in Europe as a result of the assessment of an application by the German Federal Institute for Drugs and Medical Devices (BfArM). Please provide data assessing the therapeutic impact of the formulation change or justification as to why an assessment is not necessary.
- Please provide an updated *Clinical Overview* that takes into account the available post marketing safety data for Budenofalk foam enema and that also addresses the extent to which the efficacy and safety data contained within the dossier satisfies the TGA's current requirements.

Pharmacokinetics

- Please review the following concerns about the accuracy of data presented in the BUF-7/BIO study report and where necessary re-analyse the data and present amended summary data and/or comment.... (*Background information was provided as per the evaluator's comment above*).

Safety

- Please review the summary statistics for the all the haematology and biochemistry tests in Study BUF-5/UCA and where necessary re-analyse the data and present amended summary data and/or comment (*Background information was provided as per the evaluator's comment above*). The analysis of proportions of patients with clinically significant changes needs to be re-analysed using correctly denoted data and the results presented in a meaningful manner, for example with information about how clinically significant changes were identified and presentation of results according to the direction of change (as was done for the pivotal study).
- Please review the summary statistics for the all the haematology and biochemistry tests in Study BUF-6/UCA and where necessary re-analyse the data and present amended summary data and/or comment (*Background information was provided as per the evaluator's comment above*).
- Please provide PSURs reports covering the post market experience with Budenofalk foam enema generated since its international birthday.

Evaluation of responses to clinical questions

The questions covered 5 main issues, which are addressed below.

Differences between the formulation used in clinical trials and that proposed for marketing

In response the sponsor provided a detailed comparison of the composition of the formulations with and without sorbic acid. From the analysis it was apparent that for the marketing formulation, the sorbic acid was replaced by a small amount of propylene glycol *in addition to* that already contained within the formulation used for the clinical trials. On a "per puff" basis, the amount of propylene glycol only increased from 600.00 to 600.30 mg as a result of the formulation change, which is negligibly small. The sponsor also indicated that prior to the change and in the course of follow-up activity, physicochemical bridging studies on laboratory and production scale batches were conducted to demonstrate that the sorbic acid-free formulation also met the acceptance criteria which had been established for the drug product used in clinical trials, including foam volume, duration of expansion and pH. The sponsor concluded that both quantitatively and qualitatively the changes would not have significantly

altered the physicochemical properties of the foam. This argument was accepted by the clinical evaluator and the issue has been resolved satisfactorily.

The sponsor also commented on the clinical evaluator's statement that the batch used in Study BUF-5/UCA[31] was outside the lower release specification (RS) for budesonide (93% versus RS 95-105%). The clinical evaluator's statement was based on tabulated batch analysis data presented in the submission. In response, the sponsor indicated that the data for this batch were based on re-tests and that end of shelf-life specification for the batch was in fact 90-110%, such that the assay of 93.3% was not out of specification. The table cited in support of the sponsor's argument had additional contextual information about the change of RS for the batch. Also of note, the table also showed that the RS for sorbic acid had also changed to 70-110%, such that the assay level of 83.5% for this excipient was also within specification. Consequently, it was accepted by the clinical evaluator that batch 72071 was within specification for the budesonide and sorbic acid assays and the issue has been resolved satisfactorily.

Overall, it is accepted that there would be no clinically significant difference between the efficacy and safety of batches used in the clinical development program and the product intended for supply in Australia.

Apparent errors in the presentation of PK data - Study BUF-7/BIO

In response, the sponsor re-analysed the available data and provided a *Re-evaluation Report BUF-7/BIO*. A non-compartmental approach was taken for the pharmacokinetic re-analysis, using WinNonlin Professional (Version 5.3) software for the estimation of pharmacokinetic parameters. Appropriate criteria were used for the handling of concentration values below the LLOQ (0.1ng/mL).

The re-analysis and report:

- confirmed and corrected the erroneous concentration–time curves for three subjects;
- confirmed and corrected the errors in the original within-study assay validation;
- explained that, in the original report, $AUC_{0-\infty}$ could be lower than the AUC_{0-12} for some subjects by virtue of the fact that these two figures were calculated differently; this was avoided in the re-analysis by using the more modern software; and
- found only minor differences between the re-evaluated PK parameters and those reported in the original report for BUF-7/BIO.

The key PK parameters from the re-analysis are shown in Table 24 (data from the original analysis are in Table 3) and the concentration-time plots are shown in Figure 11 (plots from the original analysis are in Figure 1). Following re-analysis, the mean C_{max} on Day 1 was 0.838 ng/mL reached about 2 h after administration, and 1.07 ng/mL reached at 1.89 h on Day 5 (p value not significant). The AUC for budesonide was slightly reduced after multiple dosing and a comparison of the logarithms of the extrapolated area under the curve on Day 1 and the area under the curve of one dosing interval on Day 5 were not statistically significant (p=0.0721). The mean apparent terminal elimination half-life was approximately 3.8 h on Day 1 and 3.4 h on Day 5. The relative bioavailability of budesonide was approximately 16.7% (CL=503 L/h) after a single dose and approximately 12.5% (CL=670L/h) after multiple doses, assuming a clearance of 83.7 L/h for intravenous budesonide as reported by Ryrfeldt et al 1982[32].

[31] Note: In the original draft of the first round evaluation report, study BUF-5/UCA had been incorrectly cited as BUF-5/BIO.

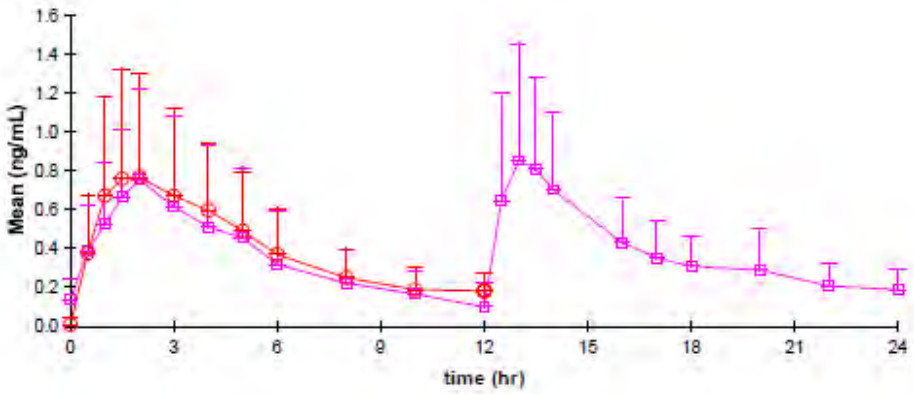
[32] Ryrfeldt A, Andersson P, Edsbäcker S, Tonnesson M, et al. Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. *Eur J Respir Dis*. 1982; **122** (Suppl.): 86-95.

Table 24. Study BUF-7/BIO - Revised mean pharmacokinetic parameters

Parameter	Mean	SD	Mean	SD	P-value t-test
Day	1		5		
N	18		18		
Dose(mg)	2		(2) 4		
AUC0_12(hr*ng/mL)	4.598	2.902	4.191	2.928	0.4584
AUCINF_obs(hr*ng/mL)	5.594	3.840	9.152	5.574	
AUCINF_D_obs(hr*ng/mL/mg)	2.797	1.920	2.288	1.393	0.2183
AUC_24(hr*ng/mL)			8.395	5.319	
AUC_ss(hr*ng/mL			4.198	2.660	0.0721
Cl_F_obs(L/min)	8.375	5.371	11.174	7.301	0.1444
Cmax(ng/mL)	0.838	0.551	1.074	0.579	0.0587
Cmax_D(ng/mL/mg)	0.419	0.276	0.536	0.290	0.0587
HL_Lambda_z(hr)	3.870	1.227	3.367	1.215	
MRTINF_obs(hr)	6.780	2.040			
Tlag(hr)	0.083	0.192	0.000	0.000	
Tmax(hr)	2.000	1.150	1.889	1.685	0.8021

Parameters including '_D' are normalized for the dose.

Figure 11. Study BUF-7/BIO – Revised mean (SD) serum budesonide concentrations after rectal administration on Days 1 and 5



The sponsor was unable to identify a biological explanation for the detectable budesonide serum concentration at base line for subject 19 on Day 1 and suggested possible reasons for this result included errors in handling of the sample in the clinic or laboratory and contamination of the sample. The sponsor noted that the contribution of the value (0.15 ng/mL) to the overall $AUC_{0-\infty}$ value was less than 0.8%, far below the variability of the AUC values.

Overall, the recalculated data were acceptable to the clinica evaluator and the conclusions of the study, that there is no significant accumulation of budesonide and that peak systemic concentrations are approximately 1 ng/mL are considered to have been supported.

Erroneous laboratory data analyses. Studies BUF-5/UCA and BUF-6/UCA

The sponsor undertook an intensive re-evaluation of the laboratory data for these two studies and found there were errors in the summary tables and listings at the data management department of the Contract Research Organisation. The errors were based on partly wrong computer programs for the laboratory data, which probably resulted from incorrect use, and incorrect transformation of different local laboratory units into standardised units for descriptive analysis. To correct the wrong data, the sponsor removed all flags (low/normal/high) the laboratory values and re-set them after checking the correct value and

unit. Where necessary, data values were transformed into a different unit for the descriptive/summary statistical analyses. The sponsor re-analysed the data as requested and prepared corrigenda for both study reports. In addition, within these corrigenda, the sponsor prepared tabular and discursive summaries of all deteriorations (even if only transient) as well as clinically relevant deteriorations, analysed by the direction of change.

In Study BUF-5/UCA, clinically significant laboratory abnormalities were present in the majority of patients thoughout the study, with the proportion of affected patients ranging from 55%-80% depending on treatment group and visit. There were no statistically significant differences between either of the budesonide treatment groups (2 mg and 4 mg) and placebo in the proportion of patients with specific clinically significant laboratory abnormalities or in the incidence of these abnormalities. The most frequently reported newly occurring deteriorations of clinical significance were:

- increased ESR: placebo 18%; BUD 2 mg 16%; BUD 4 mg 9%;
- decreased haematocrit: placebo 16%; BUD 2 mg 16%; BUD 4 mg 20%;
- decreased haemoglobin: placebo 13%; BUD 2 mg 17%; BUD 4 mg 20%;
- increased leucocytes: placebo 17%; BUD 2 mg 16%; BUD 4 mg 11%;
- increased lymphocyte counts: placebo 12%; BUD 2 mg 14%; BUD 4 mg 9%;
- increased CRP: placebo 7%; BUD 2 mg 10%; BUD 4 mg 11%;
- increased aldosterone: placebo 4%; BUD 2 mg 13%; BUD 4 mg 8%;
- increased total bilirubin: placebo 3%; BUD 2 mg 3%; BUD 4 mg 3%; and
- increased ALT: placebo 5%; BUD 2 mg 3%; BUD 4 mg 7%.

In Study BUF-6/UCA, the proportion of patients with clinically significant laboratory abnormalities was somewhat less than in Study BUF-5/UCA, with a minority of patients affected (ranging from 18%-26%, depending on treatment group and visit). In this study there were few cases of newly occurring deteriorations that were considered to be of clinical significance, with the most common being:

- increased ESR: BUD 2 mg 3%; Hydrocortisone 8%;
- decreased haematocrit: BUD 2 mg 3%; Hydrocortisone 2%;
- decreased haemoglobin: BUD 2 mg 3%; Hydrocortisone 1%; and
- increased blood glucose: BUD 2 mg 3%; Hydrocortisone 1%.

Of note, across both studies the majority of affected parameters correlated with inflammatory activity and were most often assessed as "related to ulcerative colitis" by the study investigators. The corrected summary statistics for the various laboratory parameters showed there were no clinically important changes in any of the laboratory parameters in either study. Overall, no new safety concerns were identified from the analysis of corrected laboratory data for these studies.

Absence of post marketing data for the rectal foam

In response, the sponsor provided 4 PSURs that collectively covered the period March 1998 to February 2011:

- PSUR 2003 (11 March 1998 to 31 December 2002);
- PSUR 2008 (01 January 2003 to 30 April 2008);
- PSUR 2010 (01 January 2005 to 30 April 2010); and

- PSUR 2011 (01 May 2010 to 28 February 2011).

The sponsor also submitted an updated *Clinical Overview* document that appraised these reports.

PSUR 2003 covered Budenofalk oral capsules only, as the rectal foam was first approved for marketing in 2006. The subsequent PSURs covered both the oral capsules and the rectal foam and provided an estimate of the number of treatment cycles of each formulation. Each PSUR included a line listing of all ADRs for the period covered; CIOMS forms[33] and line listings for all serious unlisted ADRs for the period; and a cumulative line listing of all serious unlisted ADRs from January 1997 to the end of the period covered. Given the overlap of the periods covered by PSUR 2008 and PSUR 2010, it is not possible to give a precise estimate of the number of treatment cycles of Budenofalk rectal foam that have been distributed since its first marketing approval. However, it appears that the figure is in excess of 50,000 treatment cycles.

There have been a total of 6 reports describing 8 ADRs associated with the use of Budenofalk rectal foam. None of the reactions were considered to be serious and unlisted. The most common reactions (n=4) have comprised cutaneous reactions; allergic exanthema (n=2); allergic skin reaction (n=1) and maculopapular exanthema (n=1). The outcome was reported as 'recovered' in all but one of the four reports and one was noted to have had a positive re-challenge. There have been single reports of hypertension, bradycardia and ankle oedema (all reported from the same patient) and pancreatitis, with an outcome of 'recovered' for both cases. In addition, there were 3 ADR reports in which the formulation was unknown; one report of an aggravation of neurodermatitis (outcome unknown), one report of ecchymosis (outcome unknown), and one report of a dystonic reaction (considered to be serious and unlisted; outcome 'recovered') in a patient also receiving azathioprine and zopiclone.

Overall, these cumulative post marketing safety data provide reassurance regarding the safety of Budenofalk rectal foam.

Reconciliation of the submission against current TGA guidelines

In response, the sponsor has assessed Studies BUF-5/UCA, BUF-6/UCA and BUF-9/UCA against the requirements of the TGA adopted guideline *Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis* (CHMP/EWP/18463/2006)**Error! Bookmark ot defined.** (see Table 25)

[33] Council for International Organizations of Medical Sciences (CIOMS) forms: Suspect Adverse Reaction Report Form

Table 25. Reconciliation of dose-finding and efficacy/safety studies against TGA requirements

Requirement of guideline	Dose finding and pivotal efficacy & safety studies		
	BUF-5/UCA	**BUF-6/UCA**	**BUF-9/UCA**
Patients included			
Diagnosis of UC			
- symptoms	y	y	y
- endoscopy	y	y	y
- histology	y	y	y
Exclusions			
- infections	y	y	y
- cancer	(Serious secondary diseases)	(Serious secondary diseases)	(Serious secondary diseases)
Further specifications			
Extent (macroscopic lesions) (Proctitis=P/Proctosigmoiditis=PS/Left-sided=LE/Extensive=E)	P, PS	P, PS (40 cm ab ano)	P, PS (40 cm ab ano)
Disease activity (mi/mo/s/st-ref)	mi-mo CAI >4 to ≤12 EI≥4	mi-mo DAI ≥4	mi-mo CAI>4 EI≥4
Histol. evidence of active UC	y	y	y
Incl. criteria previous/present therapy	New (> 2 weeks) & established diagnosis	New (> 2 weeks) & established diagnosis	New (> 2 weeks) & established diagnosis
Accessibile for rectal treatment	y	y	y
Exclusion criteria (most/some/few/none respected)	some	most	most
Baseline criteria (most/some/few/none respected)	most	most	most

Table 25 continued. Reconciliation of dose-finding and efficacy/safety studies against TGA requirements

Efficacy endpoints			
Primary efficacy endpoint (sympt/endo/comb/other)	Index (sympt)	Index (comb)	Index (sympt)
Remission (y/n)	y	y	y
Index used/Definition of remission	CAI≤4 + ΔCAI≥2	DAI≤3	CAI≤4
Symptoms (sf/ur/bs)	sf, bs	sf, bs	sf, bs
Treatment duration to remission (w)	6 w	8 w	4 w
Maintenance after induction (w)	n.a.	n.a. (median time to remission ≤ 8 days)	n.a. (median time to remission ≤ 9 days)
Secondary efficacy endpoints (most/some/few/none)	most	most	most
Indices/parameters used for secondary efficacy endpoint	EI, HI, DAI, PGA, CRP, ESR	DAI, HI, (EI), PGI	DAI, EI, PGA
Exploratory study?	IIb	no	no
Dose finding, dose-response (≥ 3 doses)	2 justified doses	n.a.	n.a.
Main therapeutic study?	(IIb)	III	III
Design (pg, r, db, pc/ac)	R, db, pg, pc	R, g, ac, open, pathologist blinded	R, db, dd, pg, ac
biomarkers	CRP, ESR	no	no
Aim/design relevant for indication? (y/n)	y	y	y
Restriction to ≤ 2 degrees of activity	y	y	y
Effects size according to activity (y/n)	y	y	y
Comparator	plac	100 mg hydrocortisone acetate OD (= standard)	2 mg/ 100ml Budesonide enema (=approved)
Comparator adequate (y/n)	y	y	y
Aim superiority/non-inferiority	superiority	ther. equival. + better safety/tolerability	ther. equival / ni acceptance
Non-inferiority delta/predefined	n.a.	no	15% suggested by authority
Double dummy design	n	n	y
Duration 8 – 12 weeks	6 w justified	8 w justified	4 w suggested by authority
Follow-up, off-treatment	-	-	-
Safety evaluation			
All AEs collected?	y	y	y
AEs documented by SOC?	y	y	y
Safety data for 1 year	n.a. / PSUR		

Ac: active controlled; bs: blood in stool; CRP: C-reactive protein; db: double-blind; E: extended colitis; EI: endoscopic index; ESR: erythrocyte sedimentation rate; HI: histological index; L : left-sided colitis; mi: mild disease activity; mo: moderate disease activity; n: no or not present; P : Proctitis; pg: parallel group design; pc: placebo-controlled; PGA: physicians global assessment; PS: Proctosigmoiditis; r: randomised; s: severe diseases activity; sf: stool frequency; st-ref: steroid-refractory course of the disease; ur: urgency; y: yes or present.

The sponsor considered that the studies satisfied, to a complete or at least a near complete extent, the requirements set by the guideline relating to the adequate selection and diagnosis of the patients included, selection of primary and secondary efficacy endpoints and safety evaluations. The clinical evaluator agreed with this assertion. The sponsor also considered that the designs of these studies also satisfied the requirements. This issue, specifically with respect to Study BUF-6/UCA, is considered under *List of Questions* below.

Evaluation of sponsor's comments on the first round evaluation report

In addition to the set of questions after the first round evaluation, the sponsor was sent a copy of the first round evaluation report. In response they provided a very detailed analysis (and rebuttal) of the three issues that formed the basis of the clinical evaluator's preliminary recommendation for rejection:

- Comparability (or perceived lack thereof) of the Colifoam preparation used in Study BUF-6/UCA and the Colifoam product available in Australia;
- The status of Study BUF-6/UCA – pivotal or supporting?; and
- Whether efficacy has been established satisfactorily for the proposed indication.

These are addressed in turn below.

Comparability of the Colifoam preparation used in study BUF-6/UCA and the Colifoam product available in Australia.

One of the main issues raised in the first round evaluation was that it appeared that the Colifoam preparation used in Study BUF-6/UCA had a different formulation that the Colifoam product available in Australia, the concern being that even small differences in the composition of such products could influence their physicochemical properties and result in differences in the extent of the active compound penetration and therefore efficacy of the product. The question was not whether hydrocortisone acetate was an appropriate comparator but rather whether the results obtained for the Colifoam product used in Study BUF-6/UCA could be extrapolated to the Colifoam product supplied in Australia.

On the basis of the overall information provided by the sponsor, the clinical evaluator was now satisfied that the Colifoam products used in the study and the Colifoam product currently supplied in Australia have comparable qualitative and quantitative composition (and therefore physicochemical properties) that should manifest in the same performance of the foam and efficacy of the product. Consequently, the results of Study BUF-6/UCA can be extrapolated to an Australian setting.

The status of Study BUF-6/UCA – pivotal or supporting?

It follows from the section above, that one of the impediments to considering BUF-6/UCA as a pivotal study has been removed, as 10% hydrocortisone is an accepted standard for treatment of left sided ulcerative colitis.

However, the clinical evaluator also expressed concern that Sstudy BUF-6/UCA was open label. This issue was raised particularly in the context of endpoints that incorporate a number of subjective measurements. The intent was not to question the validity of the subjective measures or the study endpoints but to indicate that unblinded assessment of these subjective measures inherently has more potential for bias than blinded assessment of the same measures.

In response the sponsor argued that in contrast to the use of oral formulations it was not feasible to employ a double-dummy design for a comparison of two rectal formulations because administration of both an active and a placebo rectal preparation at the same time would be impossible because of the large volumes involved and consequently retention difficulty. This argument was accepted. It was also noted by the sponsor that the central pathologist was blinded to treatment and that the results of histological assessment (an important secondary

efficacy endpoint) were congruent with the clinical and endoscopic study endpoints; and that the efficacy of Budenofalk foam observed in Study BUF-6/UCA was very similar to that observed in the double-blinded Study BUF-9/UCA, suggesting that the results obtained in Study BUC-6/UCA were not biased by knowledge of the treatment group.

Furthermore, a number of measures were adopted in the analysis of the results to ensure that the most conservative approach was used to increase the robustness and therefore confidence in the veracity of the results of the study:

- the PP analysis was prospectively chosen as the primary analysis. Consequently, exclusion of non compliers and other protocol deviations that could make the treatment estimates more equal should be more conservative in terms of proof of non-inferiority;
- a more stringent criterion (10%) was adopted for the lower boundary of the 95% CI than was actually required (11%). The choice of the lower boundary was based on the generally accepted rule that the boundary should be at least half the difference between the expected point estimate for Colifoam (40%) and the pooled placebo rate (18% based on a meta-analysis of rectal treatment with suppositories and enemas for ulcerative colitis; Su et al., 2007[34]), that is 11%. (In actuality, the rates observed for Colifoam were in 51% (PP) and 52% (ITT)); and
- premature drop outs, including those who stopped due to lack of efficacy, were analysed using their LOCF.

On a final note, the sponsor provided detailed contextual regulatory information, including aspects of their discussion with regulators from Germany and the UK in which a number of issues raised in this evaluation report were also covered. At the time the design of a second study (BUF-9/UCA, in light of the unexpected results from the dose finding Study BUF-5/UCA) was being discussed it was accepted by these regulators that Study BUF-6/UCA was a pivotal study and that BUF-9/UCA would be a second, confirmatory study.

Overall, the clinical evaluator found the sponsor's arguments persuasive and agreed that BUF-6/UCA can be accepted as a pivotal study, recognising that the study provides an inherently different level of evidence than that of Study BUF-9/UCA.

Has efficacy been established satisfactorily?

At the end of the first round evaluation, the clinical evaluator concluded insufficient data had been submitted to demonstrate the acceptable efficacy of the Budenofalk foam enema. However, since then the sponsor has, in the opinion of the clinical evaluator:

- successfully argued that the formulation changes to the product subsequent to the completion of the clinical development program were minor there would be no clinically significant difference between the efficacy and safety of Budenofalk batches used in the clinical development program and the Budenofalk product intended for supply in Australia;
- confirmed the comparability of the qualitative and quantitative composition of Australian and European Colifoam products, such that there would be no clinically significant difference between the efficacy and safety of the Colifoam product used in Study BUF-6/UCA and the Colifoam product currently supplied in Australia; and
- successfully argued that Study BUF-6/UCA is a pivotal study.

It can be considered that two pivotal studies have in fact been submitted and, contrary to the evaluator's original position, the submission does not fall under the requirements applying to a submission with one pivotal study (as outlined in *Points to Consider on Application with 1. Meta-*

[34] Su C, Lewis JD, Goldberg B, et al. A meta-analysis of the placebo response rates of remission and response in clinical trials of active ulcerative colitis. *Gastroenterology* 2007**; 132(2):** 516-26

analyses; 2. One Pivotal Study (CPMP/EWP/2330/99)). The borderline results for the tests of non-inferiority (see Table 26, below) should be re-examined in this light. As pointed out, the lower bound of the 95% CI for non-inferiority in Study BUF-6/UCA was more stringent than was actually required and the lower bound for the 95% CI for the PP analysis lay within -11%. This, in fact, also applied in Study BUF-9/UCA where, based on an expected clinical remission point estimate of 55% in both treatment groups and the pooled (meta-analysis) placebo response rate of 18% in ulcerative colitis trials, a lower boundary of the 95% CI of -18.5% would have sufficed as general rule for the demonstration of non-inferiority. The choice of a delta of 15% was quite conservative and the lower boundaries for all of the PP and ITT analyses would have fitted within a delta of -18.5%.

Table 26. Clinical remission rates for studies BUF-6/UCA and BUF-9/UCA

	Study BUF-6/UCA **No. (%) patients in remission (DAI ≤ 3) at week 8 (LOCF)**		**Study BUF-9/UCA** **No. (%) patients in remission (CAI ≤ 4) at week 4 (LOCF)**	
	BUF 2mg	**Hydrocortisone 100mg**	**BUF 2mg**	**Entocort 2mg**
PP population	n = 88	n = 91	n = 210	n = 239
No. (%) in clinical remission	48 (55%)	46 (51%)	125 (59.5%)	157 (65.7%)
Difference in proportions	4.0		-6.2	
95% CI	-10.6 to 18.6		-14.9 to 3.8	
ITT population	n = 120	n = 128	n = 256	n = 268
No. (%) in clinical remission	63 (53%)	67 (52%)	150 (56.6%)	173 (64.6%)
Difference in proportions	0.16		-8.0	
95% CI	-12.3 to 12.6		-17.0 to 0.3	

The sponsor also highlighted the fact that clinical remission rates with Budenofalk foam were quite similar across the studies (indeed they were consistently above 53%, irrespective of the analysis population) and that the patients selected and enrolled in the studies were a good representation of the actual cohort of distal ulcerative colitis patients found in day to day practice and thus mirror the target population.

Furthermore, the sponsor presented the results of a re-analysis of data generated from Studies BUF-9/UCA, BUF-6/UCA and BUF-5/UCA undertaken against more stringent criteria, which had been requested by the BfArm during their review process. These results are reproduced in Table 27 and show that the remission rates within the budesonide rectal foam groups are consistent across the studies when using stringent definitions such as "CAI<=1, DAI<=1, or DAI subscore 3=0 (that is, mucosal healing)", and that an indirect comparison of these data with available meta-analytical data for placebo (that included the unexpectedly high response rate from Study BUC-5/UCA) show a numerical superiority of the budesonide groups versus placebo

when using either the definitions pre-specified in the protocols for these studies or the more stringent definitions requested by the BfArm.

Table 27. Comparison of clinical, endoscopic and histological endpoints for Budenofalk with results from a placebo meta-analysis (all UC studies and all enema studies)

	Percentage of patients in remission / improvement at last Visit (LOCF) according to protocol definitions (ITT analysis)									
	Meta-Analysis (BUF-15)		BUF studies	BUF-5/UCA			BUF-6/UCA		BUF-9	
	All studies	All enema studies	Efficacy Criteria	2mg BUF N=70	4mg BUF N=76	Placebo N=76	2mg BUF N=120	100mg hCORT N=128	2mg BUF N=265	2mg BUD N=268
Clinical Remission			CAI ≤4	56%	65%	61%	NA	NA	57%[2]	65%[2]
			CAI ≤1	34%	40%	24%	NA	NA	31%	37%
	15% N=39	11% N=11	CAI ≤4 + ↓ ≥2	56%[2]	62%[2]	61%[2]	NA	NA	55%	63%
			DAI ≤3	54%	65%	49%	53%[2]	52%[2]	56%[2]	64%[2]
			DAI ≤1	31%	39%	22%	27%	23%	24%	31%
Clinical Improvement	30% N=55	29% N=55	CAI↓ ≥1	77%	88%	78%	NA	NA	80%[2]	84%[2]
			DAI↓ ≥1	79%	84%	80%	68%	66%	83%[2]	87%[2]
Endoscopical Remission	20% N=19	13% N=5	EI<4	43%[2]	49%[2]	40%[2]	NA	NA	52%[2]	54%[2]
			DAIsub3=0	28%	28%	21%	28%	24%	23%	27%
Endoscopical Improvement	32% N=20	27% N=4	EI↓ ≥1	66%	76%	59%	NA	NA	74%[2]	79%[2]
			DAIsub3↓ ≥1	53%	60%	59%	68%[2]	60%[2]	61%	69%
Histological Remission	9% N=9	5% N=5	HI[1]	16%	25%	21%	17%[2]	18%[2]	45%2	46%[2]
Histological Improvement	26% N=14	24% N=6	HI[1]	60%[2]	61%[2]	54%[2]	58%[2]	62%[2]	49%[2]	55%[2]

Abbreviations: BUD, Budesonide enema; BUF, Budesonide foam; CAI; Clinical Activity Index (Rachmilewitz); DAI, Disease Activity Index (Sutherland), EI, Endoscopic Index (Rachmilewitz); hCORT, Hydrocortisone acetate foam; HI, Histological Index; NA, not applicable

1 Please note that in BUF-5 and BUF-6 the HI acc. to Floren, whereas in the BUF-9 the HI acc. to Riley was used, which differ from each other.

2 Rates according to protocol definitions. All other remission/improvement rates derived from the requested post-hoc analysis.

Also, in the post hoc analysis of Study BUF-5/UCA (the dose ranging study that was considered by the clinical evaluator to be "failed") using more stringent response criteria, the clinical remission rates showed a numerical superiority of Budenofalk 2 mg and 4 mg rectal foam over placebo (CAI ≤ 1: 34% and 40%, respectively, versus 24%; DAI≤ 1: 31% and 39%, respectively, versus 22%), however the results were statistically significant only for the 4 mg dose (and not the proposed dose). Similarly, there was a numerical superiority of both doses of Budenofalk rectal foam over placebo for endoscopic remission rates, indicating mucosal healing (DAIsub3=0: 28% and 28%, respectively versus 21%), however these results were also not statistically significant, serving to underline the lack of powering in that study due to the higher than expected response to placebo.

Overall, having reviewed the additional information and arguments submitted by the sponsor, the clinical evaluator considers that the sponsor was justified in concluding that the efficacy of Budenofalk foam enema has been established in the proposed indication. The clinical evaluator was now satisfied that acceptable efficacy has been demonstrated as follows:

- the efficacy of Budenofalk 2 mg rectal foam has been demonstrated in comparison with a formulation of hydrocortisone enema that is expected to give efficacy comparable to that of the hydrocortisone formulation available in Australia (BUF-6/UCA), and that the efficacy is clinically meaningful;
- the efficacy of Budenofalk 2 mg rectal foam has been demonstrated in comparison to Entocort enema which, although not registered in Australia, was accepted as having clinically meaningful benefit over placebo (BUF-9/UCA);

- the use of Budenofalk 2 mg rectal foam has yielded consistently clinically meaningful responses across the studies undertaken in the clinical development program; and
- indirect comparison of data for Budenofalk 2 mg rectal foam with available meta-analytical data for placebo, Budenofalk has a numerical superiority versus placebo, including when more stringent criteria for clinical response are adopted.

Clinical summary and conclusions

Preliminary Benefit-Risk Assessment and Recommendations

Benefits

The benefits of sorbitol-containing Budenofalk foam enema in the proposed usage appear to be:

- a clinical remission rate (based on reduction of CAI) of approximately 50%;
- a corresponding reduction in stool frequency and blood in or on the stools; and
- a preference among patients because of its ease of handling.

However, an over riding consideration with this application is that the formulation intended for registration in Australia contains propylene glycol rather than sorbitol. Small differences in the composition (including non-active substances) of locally-applied, locally-acting products may influence their physicochemical properties and, consequently, penetration and efficacy of the active compound.[35] There were no data demonstrating the therapeutic equivalence of the pre and post 2006 formulations and no justification as to why such data were not necessary.

Even if therapeutic equivalence data or an adequate justification for not providing such data was forthcoming, the sponsor has still submitted only one confirmatory double blinded study for the sorbitol-containing formulation and they have not been reproduced in a second double blinded confirmatory study. Furthermore, no data have been submitted to demonstrate the benefits are maintained off-treatment.

Risks

The risks of budesonide in the proposed usage appear to be those associated with its gluco-corticosteroid effects.

However, the longest duration of treatment of any patient in the clinical development program was 8 weeks. Risks associated with repeated courses of Budenofalk foam over time (the treatment of repeated flares of active disease) and, particularly, local tolerability of the propellants and foam constituents, have not been assessed.

There are also apparent errors in the tabulation and analysis of IPD laboratory data (Studies BUF-5 and -6/UCA) and in the outputs of the statistical analysis package (Study BUF-6/UCA).

Benefit-Risk Balance

The benefit-risk balance of Budenofalk foam enema is unfavourable.

No data have been generated using the formulation intended for supply in Australia. The likely benefits of the sorbitol-containing formulation have not been duplicated in a second double-blinded confirmatory study. Also the safety profile has not been completely defined, particularly the risks associated with repeated use of Budenofalk foam in the treatment of recurrent flares of active disease.

[35] *Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents*, pp 193 – 198 of The Rules Governing Medicinal Products in the European Union 1998 (3C – 3CC12a)

Preliminary Recommendation Regarding Authorisation

The application to register Budenofalk (budesonide 2 mg) foam enema for the treatment of active distal ulcerative colitis, proctitis and proctosigmoiditis should be rejected on the grounds that:

- no data have been generated using the propylene glycol-containing formulation intended for registration in Australia;
- insufficient data have been submitted to confirm the acceptable efficacy and long term safety of the sorbitol-containing product; and
- the sponsor has submitted an out-of-date dossier that does not comply with the TGA's current regulatory requirements.

Final benefit-risk assessment and recommendations

Note: This final assessment of risks and benefits and the accompanying recommendations take into account any responses to clinical questions raised and evaluated in this report, as well as additional arguments made by the sponsor in its response to the evaluation report.

Benefits

After consideration of the responses to clinical questions, the benefits of Budenofalk foam enema in the proposed usage appear to be:

- a clinical remission rate (based on reduction of CAI) of approximately 50%;
- a corresponding reduction in stool frequency and blood in or on the stools; and
- a preference among patients because of its ease of handling.

Notwithstanding the differences in definitions of remission and durations of treatment, the clinical remission rates were quite similar across two pivotal studies. There were also common features across the studies with respect to analyses of remission rates by baseline covariates:

- milder episodes of ulcerative colitis were associated with higher remission rates than moderate episodes;
- localisation of disease to the rectum was associated with higher remission rates than disease also involving the sigmoid colon; and
- a longer duration of disease (more than 5 years) was associated with lower remission rates.

Risks

After consideration of the responses to clinical questions, the risks of Budenofalk foam enema in the proposed usage appear to be those associated with its gluco-corticosteroid effects.

The longest duration of treatment of any patient in the clinical development program was 8 weeks. However, post marketing surveillance data suggest a low propensity for adverse drug reactions with usage in clinical settings.

Benefit-risk balance

The benefit-risk balance of Budenofalk foam enema, given the proposed usage, was considered favourable.

Recommendation regarding authorisation

The application to register Budenofalk (budesonide 2mg) foam enema for the treatment of active distal ulcerative colitis, proctitis and proctosigmoiditis should be approved.

Enteric capsules

Introduction

Guidance

The following EU Guidelines adopted by the TGA are relevant to this submission:

- Guideline on the Development of New Medicinal Products for the Treatment of Crohn's disease (CPMP/EWP/2284/99 Rev 1);
- Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents, pp 193 – 198 of The Rules Governing Medicinal Products in the European Union 1998 (3C) – 3CC12a; and
- Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal Study (CPMP/EWP/2330/99).

Contents of the clinical submission for the enteric capsule

Data submitted in support of the registration of Budenofalk oral capsules were contained in formal study reports and published studies.

Published studies were identified from literature searches of Medline (December 2010), Embase (December 2010), and The Cochane Library (October 2010). Copies of the complete unedited search strategies, the search output and the selection criteria for inclusion of studies in the submission were provided by the sponsor. The sponsor also broaden the searches to include case reports, editorials, letters, notes and comments.

The submission contained the following clinical information:

Ten clinical pharmacology studies of budesonide capsules in adults and children, including 3 that provided pharmacokinetic (PK) data only and 7 that provided both PK and pharmacodynamic data (PD), as follows:

- 3 studies in healthy adults: BUC-5.C3 (PK/PD); BUC-5.C9/BIO and BUC-5.C18/BIO* (PK/PD); BUC-59/BIO [Ufer et al 2008[36]]** (PK);
- * BUC-5.C9/BIO & BUC-5.C18/BIO was presented as a single study report
- ** The pharmacogenetic component of BUC-59/BIO was published by Ufer 2008.
- 2 studies in healthy adults examining the effect of food on pharmacokinetics of Budenofalk capsules: BUC-5.C3 NBF_BF (PK); BUC-5.C9 NBF_BF (PK);
- 2 studies of Budenofalk capsules in adult patients with active inflammatory bowel disease: BUC- 14/BIO (PK/PD); Kolkman et al 2004[37] (PK/PD);
- 1 study in adult patients with hepatic impairment (primary biliary cirrhosis): Hempfling et al 2003[38] (PK/PD); and

[36] Ufer M, Dilger K, Leschhorn L, et al. Influence of CYP3A4, CYP3A5, and ABCB I genotype and expression on budesonide pharmacokinetics: A possible role of intestinal CYP3A4 expression. *Clin Pharmacol Ther* 2008: **84**: 43-6.

[37] Kolkman JJ, Mollmann HW, Mollmann AC, et al. Evaluation of oral budesonide in the treatment of active distal ulcerative colitis. *Drugs Today* (Barc) 2004; **40(7)**: 589 -601.

[38] Hempfling W, Grunhage F, Dilger K, et al. Pharmacokinetics and pharmacodynamic action of budesonide in early- and late stage primary biliary cirrhosis. *Hepatology* 2003: **38(1)**: 196-202.

- 2 studies in paediatric patients with Crohn's disease: BUC-48/BIO (PK); Lundin et al 2003[39] (PK).
- 2 company sponsored Budenofalk dose-finding studies: BUC-15/CDA, BUC-16/CDA. These studies also examined the dose- PD response effects of Budenofalk on the HPA axis and bone metabolism.
- For the treatment of *active Crohn's disease*:
  - In adults:
    - 4 exploratory efficacy/safety studies: 2 company-sponsored studies (BUC-15/CDA, BUC-16/CDA) and 2 published studies (Gross et al 1996[40], Caesar et al 1997[41]);
    - 2 confirmatory efficacy/safety studies, both company-sponsored: BUC-23, BUC-52/CDA;
    - 8 supporting efficacy/safety studies in adults involving the use of Entocort: Greenberg et al 1994[42], Tremaine et al 2002[43], Rutgeerts et al 1994[44], Campieri et al 1997[45], Tursi et al 2006[46], Van Ierssel et al 1995[47], Thomsen et al 1998[48], Lofberg, Danielsson and Salde 1993[49];
    - 4 meta-analyses (Papi et al 2000[50]; Otley and Steinhart 2005[51], Otley and Steinhart 2008[52], Seow et al 2008[53]) and 1 systematic literature review (Kane et al 2002[54]) of studies evaluating the effectiveness of budesonide.

[39] Lundin PDP, Edsbäcker S, Bergstrand M, et al. Pharmacokinetics of budesonide controlled ileal release capsules in children and adults with active Crohn's disease. *Aliment Pharmacol Ther* 2003; **17(l)**: 85-92.

[40] Gross V, Andus T, Caesar I, et al, and the German/Austrian Budesonide Study Group. Oral pH-modified release budesonide versus 6-methylprednisolone in active Crohn's disease. *Eur J Gastroenterol Hepatol* 1996; **8(9)**: 905-9.

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[49] Lofberg R, Danielsson A, Salde L. Oral budesonide in active Crohn's disease. *Aliment Pharmacol Ther* 1993; 7: 611-616.

[50] Papi C, Luchetti R, Gili L et al. Budesonide in the treatment of Crohn's disease: a meta-analysis. *Aliment Pharmacol Ther* 2000; **14**: 1419-1428.

- In adolescents:
  - 2 pivotal studies: 1 company sponsored study (BUC-47/CDA) and 1 published study (Levine et al 2003[55]);
  - 3 published supporting efficacy/safety studies: one of which (Levine, et al 2002[56]) reported the use of Budeson (the trade name for Budenofalk in Israel) and two which were conducted using Entocort (Escher 2004[57], Kundhal, et al 2001[58]).
- For the treatment of *collagenous colitis*:
  - 1 company-sponsored efficacy/safety study: BUC-35;
  - 2 published supporting randomised, controlled studies using Entocort: Bonderup et al 2003[59], Miehlke et al 2002[60];
  - 9 published supporting non-controlled trials, retrospective reviews, case series/reports: Boh[61] et al 1996, Bonderup and Hansen 2005[62], Chopra et al 2006[63],

[51] Otley A, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub2.

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[60] Miehlke S, Heymer P, Bethke B, et al. Budesonide treatment for collagenous colitis - A randomized, double-blind, placebo controlled, multicenter trial. *Gastroenterology* 2002; **123(4)**: 978-84.

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[62] Bonderup OK, Hansen JB. Budesonide treatment of collagenous colitis - Retrospective analysis of 99 cases. *Gut* 2005; **54 (Suppl VII)**: A179.

[63] Chopra A, Pardi DS, Loftus Jnr EV et al. Budesonide in the Treatment of Inflammatory Bowel Disease: The First Year of Experience in Clinical Practice. *Inflamm Bowel Dis* 2006; **12**: 29-32.

Delarive et al 1998[64], Janetschek and Böckmann 1998[65], Lanyi et al 1999[66], Miehlke et al 2005[60], Tromm et al 1999[67] and Fernandez-Banares et al 2003[68];

- § 2 supportive clinical trials for maintenance of remission with Entocort: Miehlke et al 2008[69], Bonderup et al 2009[70];
- § Published retrospective analyses of pooled data - by the Cochane Inflammatory Bowel Disease Group: [71, 72, 73, 74, 75] and a U.S. group (Feyen et al 2004[76]): and a systematic review of microscopic colitis by Nyhlin et al in 2006[77].
- § 1 company-sponsored supporting clinical trial in patients with lymphocytic colitis: BUC-44/LMC;

· Post marketing experience in the form of 2 Periodic Safety Update Reports (PSURs) dated 2003 (covering the period International birthday to December 31 2002) and 2008 (covering the period 1 January 2003 to 30 April 2008) and a case line listing of all adverse drug reaction reports for the period 1 May 2008 to 15 November 2009.

[64] Delarive J, Saraga E, Dorta G, Blum A. Budesonide in the treatment of collagenous colitis. *Digestion* 1998: **59(4)**: 364-6.

[65] Janetschek P, Böckmann U. Budesonide - A new highly effective therapeutic approach to collagenous colitis. *Digestion* 1998; **59 Suppl 3**: 159.

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[67] Tromm A, Griga T, Möllmann HW, et al. Budesonide for the treatment of collagenous colitis - First results of a pilot trial. *Am J Gastroenterol* 1999; **94(7)**: 187l -5.

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[76] Feyen B, Wall GC, Finnerty EP, et al. Meta-analysis - Budesonide treatment for collagenous colitis. *Aliment Pharmacol Ther* 2004; **20(7)**: 745-9.

[77] Nyhlin N, Boh J, Eriksson S, Tysk C. Systematic review: microscopic colitis. *Aliment Pharmacol Ther*. 2006: **23(11)**: 1525-34.

Evaluator's comment

The sponsor considered all 4 exploratory and 2 confirmatory studies in patients with adult Crohn's disease to be pivotal to the application for that indication. In the opinion of the clinical evaluator 3 of the 4 exploratory studies are at best supporting studies because they were low powered studies and failed to provide convincing results. For example:

- The placebo controlled dose finding study (BUC-16/CDA) failed to demonstrate any statistically significant differences in clinical response rate from placebo at the proposed 9 mg daily dose and, of the doses examined (3 mg, 9 mg and 18 mg daily), only Budenofalk 3 mg daily was shown to be statistically significantly better than placebo in the treatment of active Crohn's disease in terms of remission rates and therapeutic benefit;
- The study by Gross et al 1996[40] had 73% power to detect a 30% difference in response rates at the T0.05 significance level and much less power to detect a smaller and clinically relevant difference between the Budenofalk and 6-methylprednisolone. Consequently, the observed between-group difference in response rates of 16.8% was not statistically significant. The small sample sizes used in the study are reflected in both the width of the 95%CI for the Budenofalk response rate (37.9 to 72.8%) and the between-group difference (-5.7 to 39.3%, calculated by the clinical evaluator); and
- The study by Caesar et al 1997[41] was open label and uncontrolled. Such studies are known to be subject to observer and measurement bias and regression to the mean, and are known to overstate the true treatment effect.

These studies are critiqued further below. The sponsor also submitted two efficacy/safety studies considered by the sponsor to be pivotal in relation to use of Budenofalk in adolescent Crohn's disease: one company sponsored study BUC-47/CDA and one published paper (Levine et al 2003[55]). The clinical evaluator does not agree with the categorisation of the study by Levine et al 2003 as a pivotal study, essentially because of its open-label design and the very small patient numbers enrolled (see below).

Other main issues with respect to the contents of the clinical submission were:

- a number of published papers, based on company-sponsored studies of Budenofalk have been submitted instead of full study reports;
- numerous published studies on the efficacy/safety of Entocort have been submitted as supporting data for each of the indications sought.

Use of published accounts rather than full study reports for company-sponsored trials

The journal paper by Gross et al 1996[40] was derived from BUC-2/CDA; Caesar et al 1997[41] from BUC-4/CDA, Kolkman et al 2004[37] from BUC-18/BIO, and Hempfling et al 2003[38] from BUC-39/BIO. The sponsor submitted the 4 literature articles in preference to the full study reports in order to keep the clinical documentation to what it considered to be a reasonable size[78]. Full study reports were said to be available on request. The limitations of published papers are well known and may include inadequate reporting of methods and safety monitoring and inadequate validation of analytical methods and ethics certification. Generally, submitting published papers in order to limit the submission size is not an acceptable justification, especially when a formal company report for the study exists. Two of these studies (Gross et al 1996 and Caesar et al 1997) were claimed by the sponsor to be pivotal to the demonstration of efficacy and safety of Budenofalk oral capsules in the treatment of active adult Crohn's disease. However, these studies were small and exploratory in nature and furthermore the study by Caesar was open label, which is more in keeping with supporting studies. Thus, the absence of full company

[78] Sponsor comment: The reason for not submitting the full study reports was mainly that these studies were considered to be of minor relevance, that is, a different formulation or a different indication.

reports for these studies is not so critical. The limitations of the papers by Gross et al and Caesar et al are discussed further below.

Use of published data for Entocort to support the Budenofalk submission

The sponsor justified the use of data for Entocort in support of Budenofalk on the basis that:

- the principal release pattern of both preparations "appears to be similar" with respect to the topical anti-inflammatory effects on the mucosa and the bowel wall and that a considerable proportion of budesonide from both formulations reaches the colon and exerts its therapeutic action in this section of the gut; and
- all the available publications, meta-analyses and reviews of the role of budesonide in Crohn's disease and microscopic colitis indicate the two brands of oral budesonide are "similar in efficacy".

These arguments belie the fact that there has been no head-to-head comparison of the pharmacokinetics, pharmacodynamics, efficacy or safety of Entocort and Budenofalk for any of the indications sought. In the view of the clinical evaluator, the sponsor's arguments are inadequate because:

- the products have a different dissolution profile (Entocort dissolution commencing at pH >5.5 compared to >6.4 with Budenofalk);
- in order to prevent complete dissolution of Entocort in proximal parts of the small intestine, the release of budesonide is additionally retarded by an ethylcellulose membrane; and
- Budenofalk and Entocort are intended to be released (in essence applied locally) and act locally in the terminal ileum and colon. Thus, the relevant TGA-adopted EU guideline[79] is of some relevance in this regard. That guideline requires that therapeutic *equivalence* (not similarity) be shown.

This issue is not a major concern with respect to the proposed indication of adult Crohn's disease because the exploratory and confirmatory studies were all conducted using Budenofalk.

Good clinical practice (GCP)

Studies were carried out in accordance with ethical and scientific/GCP standards in force at the time, namely:

- The Declaration of Helsinki concerning medical research in humans (adopted by the 18th World Medical Assembly, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989 and Somerset, South Africa 1996): and
- The EU Guidelines (CPMP) on Good Clinical Practice for Trials on Medicinal Products in the European Community 1991and the ICH recommendations implemented January 1997.

Pharmacokinetics

Studies providing pharmacokinetic data

An extended biopharmaceutical development program was undertaken for Budenofalk oral capsules. The program included 68 healthy adults, 12 adults with Crohn's disease and 19 patients with hepatic impairment (Table 28). Almost all study participants were Caucasian.

[79] Note for Guidance Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents (pp 193 – 198 of The Rules Governing Medicinal Products in the European Union 1998 (3C – 3CC12a)). http://www.tga.gov.au/pdf/euguide/vol3cc12aen.pdf

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration. However, concerns were raised with respect to the presence of detectable levels of budesonide in plasma prior to dosing, which suggested the possibility of interference with the assay from either endogenous or other exogenous compounds in studies BUC-5.C3 and BUC-5.C9/BUC-5.C18.

Table 28. Submitted pharmacokinetic studies for Budenofalk oral capsules.

PK topic	Subtopic	n	Study ID	*
PK in healthy adults	General PK			
	Single dose	14 18	BUC-5.C9/BIO & BUC-5.C18/BIO BUC-59/BIO	* *
	Multi-dose	12	BUC-5.C3	*
	Food effect	12 12	BUC-5.C3 NBF_BF BUC-5.C9 NBF_BF	* *
PK in special populations	Target population §			
	Crohn's disease - *Adults*			
	Single dose		No studies	
	Multi-dose	12	BUC-14/BIO	*
	Hepatic impairment	19	Hempfling 2003 (BUC-39)	*
	Elderly		No studies	
	Other – Ulcerative colitis	15	Kolkman et al 2004 (BUC-18)	*
Genetic/gender -related PK		18	Ufer et al, 2008 (BUC-59/BIO)	*
PK interact'ns			No studies	
Population PK analyses	Healthy subjects		No studies	
	Target population		No studies	

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Summary of pharmacokinetics capsules

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

Physicochemical characteristics of the active substance and product

The following information is derived from the sponsor's summaries.

Physicochemical properties of the modified release coating

The aim of developing the gastric resistant capsule formulation was to provide topical administration, increase local efficacy and reduce systemic drug absorption. Enteric coating of the pellets with a variety of mixtures of polyacrylates of different degrees of solubility was used and dissolution was investigated under conditions simulating those of the intestine, respectively. The sponsor found an optimal formulation for the ileal release capsule.

The coating of Budenofalk enteric capsules resists dissolution in gastric juice but dissolves under conditions found in the small intestine.

Pharmacokinetics in healthy subjects

Various analytical methods were used to measure concentrations of budesonide in serum or plasma and therefore describe its pharmacokinetics.

For reasons of better specificity and to permit comparability of results across the studies submitted, budesonide PK data presented in the following sections are those obtained by HPLC/RIA unless otherwise specified[80]. The key pharmacokinetic parameters for budesonide, measured after oral administration of Budenofalk capsules to healthy subjects are summarised in Table 29.

Table 29. Summary PK parameters (mean ± SD) for Budenofalk in fasting healthy subjects

PK parameters	BUC-5.C3	BUC-5.C9/BIO & BUC-5.C18/BIO	BUC-5.C9 NBF_BF	BUC-59/BIO
	3×3 mg (N=12)	1×9 mg (N=8)	1×9 mg (N=11)	1×9 mg (N=18)
T_{lag} (h)	2.5 ± 1.3	5.00 ± 2.39	2.1 ± 1.0	2.89 ± 1.46
$T_{max\ 1}$ (h)	5.8 ± 1.6	8.50 ± 1.07	5.4 ± 1.4	6.03 ± 2.15
$T_{max\ 2}$ (h)	14.7 ± 1.5	–	–	–
$T_{max\ 3}$ (h)	23.5 ± 0.9	–	–	–
$C_{max\ 1}$ (ng/mL)	1.03 ± 0.45	2.50 ± 1.18	3.6 ± 1.3	2.16 ± 1.40
$C_{max\ 2}$ (ng/mL)	0.82 ± 0.33	–	–	–
$C_{max\ 3}$ (ng/mL)	0.70 ± 0.38	–	–	–
$C_{max\ 1-3}$/D (ng/mL/mg)	0.29 ± 0.09	0.28 ± 0.13	0.4 ± 0.1	–
AUC_{0-8h} (ng×h/mL)	3.6 ± 1.8	–	–	–
AUC_{8-16h} (ng×h/mL)	3.7 ± 1.2	–	–	–
AUC_{16-24h} (ng×h/mL)	4.0 ± 2.1	–	–	–
AUC_{∞} (ng×h/mL)	13.5 ± 4.9	13.39 ± 2.55	17.9 ± 5.8	11.72 ± 6.03
AUC_{∞}/D (ng×h/mL/mg)	1.5 ± 0.5	1.49 ± 0.28	2.0 ± 0.6	–
CL/f (L/min)	12.5 ± 4.4	11.56 ± 2.19	9.2 ± 3.0	14.93 ± 8.07
$t_{½}$ (h)	2.6 ± 1.3	4.61 ± 5.38	3.8 ± 0.9	3.71 ± 1.70
K_e (1/h)	0.328 ± 0.157	0.24 ± 0.10	0.19 ± 0.05	–
MRT (h)	7.9 ± 2.3	14.4 ± 9.3	8.9 ± 1.5	–

[80] Sponsor comment: The PK data in BUC-59/BIO were obtained by HPLC/MS/MS

Absorption

After oral administration of Budenofalk capsules, appearance of budesonide in the systemic circulation occurs with a lag time of approximately 2 to 3 h, consistent with the pH-dependent delayed release characteristics of the pellets within the capsules. The lag time was similar when Budenofalk was given in a 3 mg three times a day (tid) regimen (BUC-5.C3) or as 9 mg once daily (BUC-5.C9 NBF_BF, BUC-59/BIO). However, in Study BUC-5.C9 /BIO & BUC-5.C18/BIO single 9 and 18 mg doses were associated with longer lag times of approximately 5 h.

Peak concentrations of budesonide were observed at 6 to 7 h after administration of each single dose in a 3 mg tid regimen (BUC-5.C3), compared to 5 to 6 after administration of a single 9 mg dose (BUC-5.C9 NBF_BF, BUC-59/BIO). The somewhat later time to peak concentrations in BUC-5.C9 and BUC-5.C18/BIO of approximately 9 h is consistent with the longer lag time.

The reason for the longer lag time with higher doses was not elucidated. However, it is important to note that dose-corrected AUC estimates (AUC/D) in Studies BUC-5.C3 and BUC-5.C9 and BUC-5.C18/BIO did not differ between the treatments (3x3, 1x9 and 1x18 mg).

Bioavailability

No clinical studies of the systemic bioavailability of budesonide after administration of Budenofalk oral capsules have been performed. However, oral bioavailability was estimated in a number of the submitted studies using clearance, as calculated from the overall AUC and literature values of systemic clearance after intravenous administration of budesonide (Ryrfeldt 1982[17]; Lundin et al 2003[81]. Table 30 summarises the calculated bioavailability estimates.

Oral bioavailability was estimated at 11% in healthy subjects receiving 3 mg tid (Sstudy BUC-5.C3), consistent with the range of values (11 to 15%) obtained for a single 9 mg fasting dose (Studies BUC-5.C9/BIO and BUC-5.C18/BIO; BUC-5.C9 NBF_BF, BUC-59/BIO).

Table 30. Summary of estimated oral bioavailability of budesonide across PK studies with Budenofalk

Study	Population	Dose	Estimated oral bioavailability
BUC-5.C3	Healthy adults	9 mg (3 mg TID) on 1 study day	11%
BUC-5.C3 NBF_BF	Healthy adults	Single dose of 3 mg	11% (breakfast) 23% (no breakfast)
BUC-5.C9/BIO & BUC-5.C18/BIO	Healthy adults	Single dose of 9 mg or 18 mg	11–12%
BUC-5.C9 NBF_BF	Healthy adults	Single dose of 9 mg	12% (breakfast) 15% (no breakfast)
BUC-59/BIO	Healthy adults	Single dose of 9 mg	13% [a]
BUC-14/BIO	Adult patients with Crohn's disease	9 mg/day (3 mg TID) for at least 1 week	13%
Kolkman 2004	Patients with distal ulcerative colitis	9 mg/day (3 mg TID or 9 mg QD) for 8 weeks (or 4 weeks in case of remission)	7% (3 mg TID) 14% (9 mg QD)

[a] Sum of 11.58% for 16α-hydroxyprednisolone and 1.46% for 6ß-hydroxybudesonide excreted in urine
QD: once daily; TID: three times daily

[81]Lundin PDP, Edsbäcker S, Bergstrand M, et al. Pharmacokinetics of budesonide controlled ileal release capsules in children and adults with active Crohn's disease. *Aliment Pharmacol Ther* 2003; **17(l)**: 85-92.

Influence of food

Administration of single doses of 3 mg and 9 mg Budenofalk with food was associated with prolongation of the lag time for appearance of budesonide in the systemic circulation by approximately 2.3 h (from 2.0 to 4.3 h) for the 3 mg dose (p=0.003) and 1.7 h (from 2.1 to 3.8 h) for the 9 mg dose (p=0.0244). This is consistent with the effect of food delaying the passage of the budesonide pellets from the stomach into the duodenum. Correspondingly, t_{max} was also significantly increased from 4.8 to 7.6 h for the 3 mg dose (p=0.007) and from 5.4 to 7.6 h for the 9 mg dose (p=0.0008).

Following the intake of a single dose of 3 mg Budenofalk with food, compared to the fasting state the AUC for budesonide was significantly decreased from 9.4 to 6.0 ng.h/mL (p=0.016) and clearance (CL/f) was significantly increased from 6.0 to 12.7 L/min (p=0.003). There was also a trend toward a decrease in C_{max} (from 1.8 ng/mL to 1.1 ng/mL), although this was not significantly significant. Similar but less marked (and statistically non significant) effects were observed for the effects of food on a single 9 mg dose of Budenofalk; the AUC decreased from 17.9 ng.h/mL to 14.9 ng.h/mL, clearance increased from 9.2 L/min to 11.9 L/min and C_{max} decreased from 3.6 ng/mL to 2.6 ng/mL.

Dose proportionality

The pharmacokinetics of budesonide are linear. C_{max} for budesonide following Budenofalk administration was proportional to the single doses given and AUC values were proportional to the total daily dose. $AUC_{0-\infty}$ was comparable between the 3 mg tid and 9 mg od regimen. Dose-corrected AUC estimates (AUC/D), as calculated in studies BUC-5.C3 and BUC-5.C9/BIO and BUC-5.C18/BIO did not differ between the treatments (3x3, 1x9 and 1x18 mg).

Bioavailability during multiple-dosing

This was not assessed beyond 3 x 3 mg doses over 24 h in Study BUC-5.C3, where it was estimated to be 11%.

Distribution

No data were submitted.

Metabolism

Sites of metabolism and mechanisms/enzyme systems involved

Budesonide is metabolised in the wall of the small intestine and in the liver by isoenzymes within the CYP3A subfamily of the cytochome P450 enzyme system (Jönsson 1995[82], Seidegard 2008[83]). After oral administration, approximately 90% of the absorbed drug is eliminated by an extensive first-pass effect (Möllmann 1996[84]).

[82] Jönsson G, Aström A, Andersson P. Budesonide is metabolized by cytochome P450 3A (CYP3A) enzymes in human liver. *Drug Metab Dispos* 1995; **23(1)**: 131-42.

[83] Seidegard J, Nyberg L, Borga O. Presystemic elimination of budesonide in man when administered locally at different levels in the gut, with and without local inhibition by ketoconazole. *Eur J Pharm Sci*. 2008; **35(4)**: 264-70.

[84] Möllmann HW, Barth J, Hochhaus G, et al. Principles of topical versus systemic corticoid treatment in inflammatory bowel disease. In: Möllmann HW, May B, editors. Glucocorticoid therapy in chronic inflammatory bowel disease - from basic principles to rational therapy. FS73B ed. Dordrecht, Boston, London: Kluwer Academic Publishers: 1996. p42-60.

Metabolites identified in humans

The main metabolites of budesonide are 16α-hydroxy-prednisolone and 6β-hydroxybudesonide. The glucocorticoid activity of these metabolites are <1-10% that of budesonide (Ryrfeldt 1982[17]).

Pharmacokinetics of metabolites

Following a single oral dose of 9 mg budesonide, the mean (geometric) C_{max} for the major metabolite 16-α-hydroxy-prednisolone was 23.1 ng/mL, the median t_{max} was 5.45 h, the $AUC_{0-\infty}$ was 119.2 ng.h/mL (geometric mean), the volume of distribution 284 L (geometric mean) and the total plasma clearance was 1268 mL/min. The terminal half-life was 2.97 h.

The mean (geometric) C_{max} for 6-β-hydroxy-budesonide (2.80 ng/mL) was substantially lower than for 16-α-hydroxy-prednisolone and also occurred with a median t_{max} of 5.5 h, the $AUC_{0-\infty}$ was 25.5 ng.h/mL (geometric mean), the volume of distribution (geometric mean) 2697 litres and the total plasma clearance 6371ml/min. The terminal half-life was 5.37 h (BUC-59/BIO).

Note: Results reported for Study BUC-59/BIO were generated using an HPLC/MS/MS assay for determination of drug levels.

Consequences of genetic polymorphism

Budesonide is a CYP3A substrate. The pharmacokinetics of budesonide and its two major, inactive metabolites 16α-hydroxy-prednisolone and 6β-hydroxybudesonide in healthy volunteers was shown to be influenced by intestinal CYP3A4 expression (Ufer et al 2008[36], see Figure 12). Therefore, severe liver diseases or concomitant treatment with a potent CYP3A4 inhibitor may possibly enhance the oral bioavailability of budesonide and thereby increase the risk of corticosteroid-mediated adverse drug reactions.

Budesonide metabolism was unaffected by expression of CYP3A5 which is hepatically expressed in only 10–30% of Caucasians due to genetic polymorphism (Ufer et al 2008[36], see Figure 13).

Figure 12. Correlation of AUC_{0-24} of budesonide and partial metabolic clearances of 16-OH-prednisolone and 6-OH-budesonide with mean intestinal CYP3A4 messenger RNA expression (Ufer et al 2008)

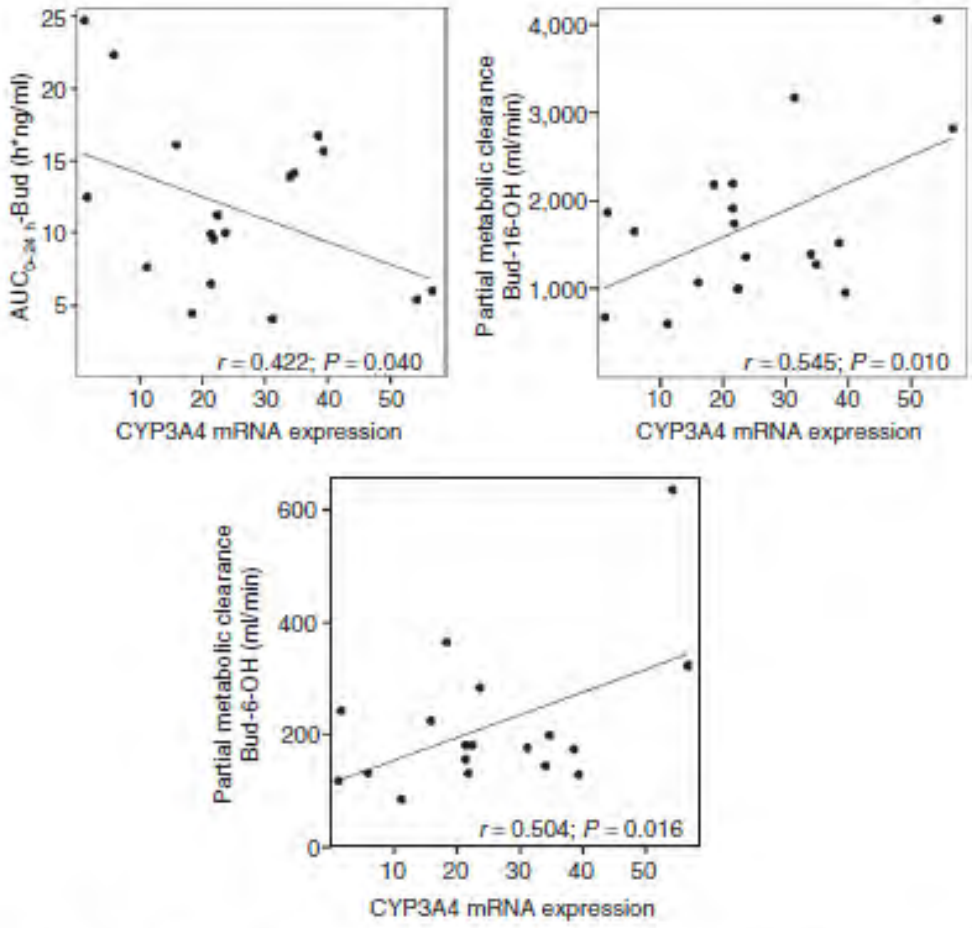
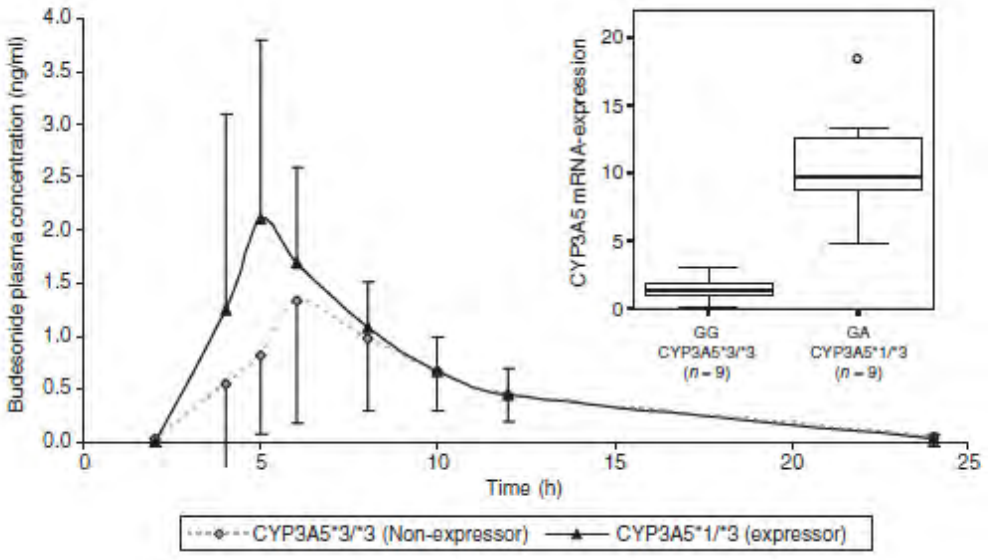


Figure 13. Budesonide plasma concentration-time curves and box and whisker plots of CYP3A5 expression levels in CYP3A5 expressors (*1/*3) and non-expressors (*3/*3) (Ufer et al 2008)



Budesonide has also been shown to be a substrate of the most prominent drug transporter P-glycoprotein encoded by the polymorphic ABCB1 gene (Dilger et al 2004[85]). However, budesonide PKs was not influenced by ABCB1 genotype or expression (Ufer et al 2008[36]).

Note: the data reported by Ufer et al 2008[36] were based on drug levels determined using an HPLC/MS/MS assay.

Excretion

The main route of excretion of budesonide is hepatic metabolism. Approximately 11.6% of a total 9 mg dose of budesonide was recovered in urine in form of 16α-hydroxy-prednisolone and 1.5 % in form of 6β-hydroxy-budesonide (Study BUC-59/BIO). Renal excretion of budesonide could be quantified in only 3/18 subjects, in each instance just above the LLOQ. Out of an apparent total clearance of budesonide of 14926 mL/min, 1749 mL/min could be attributed to a conversion into 16α-hydroxy-prednisolone and 216 mL/min to a conversion into 6β-hydroxy-budesonide.

Intra- and inter-individual variability of pharmacokinetics

There is considerable inter-individual variability in the pharmacokinetics of budesonide administered as Budenofalk capsules. The most marked variability was observed in Study BUC-59/BIO where the geometric coefficient of variation for the $AUC_{0\text{-last}}$ of budesonide following a single 9 mg dose was 78.2% and more than 45% for each of the two main metabolites. In the same study the geometric CV for the budesonide C_{max} was 82.2% and in excess of 53% for each of its metabolites. Similarly, the t_{max} demonstrated considerable variability, with a range of 3.95 to 11.83 h for budesonide and approximately 4 to 9.95h for the two main metabolites. This study used an HPLC/MS/MS assay for determination of budesonide and metabolite concentrations. The remaining studies in healthy volunteers employed the HPLC/RIAS assay for determination of budesonide concentrations. The AUC CVs ranged from 19% (BUC-5.C9/BIO) to 75% (BUC-5.C3 NBF_BF); the C_{max} CV ranged from 36% (BUC-5.C9 NBF_BF) to 81.8% (BUC-5.C3 NBF_BF); and the t_{max} CV ranged from 9.8% (BUC-5.C18) to 30% (BUC-5.C3 NBF_BF). Food did not have an appreciable impact on the PK inter-individual variability in Studies BUC-5.C3 NBF_BF or BUC-5.C9 NBF_BF.

There were limited data to enable assessment of intra-individual variation, as only one multiple dose study was performed in 12 healthy volunteers (BUC-5.C3). For some volunteers there was marked variation in the serum concentration-time curves over the three successive 3 mg doses. Intra-individual responses could be very different.

Pharmacokinetics in the target population

The pharmacokinetics of budesonide were assessed after administration of Budenofalk 3 mg capsules every 8 h over 24 h at steady state in 12 adult patients (6 male and 6 female) with active Crohn's disease (Study BUC-I4/BIO).

The PK profile and key parameters are contrasted with the results of Study BUC-5.C3, in which healthy subjects where dosed *de novo* (not at steady state) with the same regimen in Table 31. Oral bioavailability was estimated to be 13%, which is consistent with estimates in healthy volunteers. Furthermore, with the exception of terminal half-life, the PK of budesonide in patients with Crohn's disease did not differ appreciably from the PK in healthy subjects. An estimation of exact absorption delay was not possible in Study BUC-I4/BIO because of high pre-

[85] Dilger, K., Schwab, M. & Fromm, M.F. Identification of budesonide and prednisone as substrates of the intestinal drug efflux pump P-glycoprotein. *Inflamm. Bowel Dis.* 2004; **10**: 578–583.

dose budesonide levels (patients were pre-treated for at least 1 week prior to study entry). However, the absorption kinetics was similar as shown by the comparable t_{max} values. C_{max} values were slightly higher for the patient group, but the differences between the 2 populations were not statistically significant. Also, the average AUC obtained for one dosing interval in Study BUC-14/BIO was similar to AUC estimates in healthy subjects. Consequently, CL/f estimates were also not significantly different.

Table 31. Comparison of HPLC/RIA based PKs in healthy volunteers (BUC-5.C3) and adults with Crohn's disease (BUC-14/BIO)

Parameter		Volunteers HPLC-RIA		Patients HPLC-RIA	
		MEAN	S.D.	MEAN	S.D.
Dose	(mg)	9		9	
$t_{1/2}$	(h)	2.6	1.3	4.3	2.1
k_e	(1/hr)	0.328	0.157	0.184	0.060
AUC_{-0-8h}	(ng/ml*h)	3.6	1.8	8.0	5.5
AUC_{-8-16h}	(ng/ml*h)	3.7	1.2	6.7	4.0
AUC 1_{6-24h}	(ng/ml*h)	4	2.1	6.3	4.3
$AUC_{-0-9-oo}$	(ng/ml*h)	5.7	3.3		
AUC h	(ng/ml*h)			7.03	4.38
CL/F	(L/min)	12.5	4.4	10.8	8.0
T_{MAX1}	(h)	5.8	1.6	5.0	1.9
T_{MAX2}	(h)	14.7	1.5	14.5	1.6
T_{MAX3}	(h)	23.5	0.9	23.1	1.4
C_{MAX1}	(ng/ml)	1.03	0.45	1.55	1.09
C_{MAX2}	(ng/ml)	0.82	0.33	1.36	1.53
C_{MAX3}	(ng/ml)	0.7	0.38	1.39	1.12

Budesonide PK data were also presented for 13 patients with ulcerative colitis (Kolkman et al 2004[37]). Although this is not a target population for this application it provides further insight into the potential impact of IBDs on the PK of budesonide when administered in an enteric coated formulation. Kolkman et al found that the 9 mg daily regimen had slower absorption rates and higher peak levels than the 3 mg thice daily regimen, which was consistent with the studies in healthy volunteers (Tables 29 and 30). However, the finding that the once daily regimen also resulted in higher bioavailability and larger AUC than the tid regimen was in contrast with the findings of studies in healthy volunteers. The authors postulated that this may be due to differences in ethnic composition or a saturable first pass metabolism effect. Comparisons with data in healthy volunteers must be made with caution because the data reported by Kolkman et al were generated after pre treatment. In addition, in the Kolkman study for the "tid" regimen the capsules were ingested at 5 hourly intervals on the day of PK profiling and levels were assayed using an HPLC/MS/MS assay. Also of note, is that the estimated bioavailability with the 3 mg tid regimen (7%) was somewhat lower than estimated for the tid regimen in healthy volunteers (11% in BUC-5.C3) and Crohn's disease (13% in BUC-14/BIO).

Concentrations of budesonide in biopsy samples of adult patients with active distal ulcerative colitis after 56 days of treatment indicated that active drug reaches even distal regions of the colon (Kolkman et al 2004[37]).

The considerable interindividual variability observed in the PKs of budesonide in healthy volunteers was also evident from the CVs for AUC, C_{max} and t_{max} observed in studies of patients with Crohn's disease and ulcerative colitis.

Pharmacokinetics in other special populations

Subjects with impaired hepatic function

Severe hepatic impairment, as manifesting in Stage III/IV primary biliary cirrhosis (PBC), was shown to result in markedly elevated budesonide levels associated with the potential for serious ADRs (Hempfling et al 2003[38]). Contributing factors for impairment of budesonide metabolism in such a patient population include hepatocellular damage, low portal venous blood flow and intrahepatic shunting. Budesonide has a high hepatic extraction ratio, thus its hepatic clearance is most sensitive to changes in hepatic blood flow. The changes to blood flow and metabolism associated with advanced cirrhosis would not exist with Crohn's disease alone. A more likely scenario would be mild/moderate impairment. In this regard, the article noted that the pharmacokinetic parameters observed Stage I/II PBC were similar to those obtained in healthy volunteers in other studies.

Subjects with impaired renal function

No data were submitted. Given the minimal renal excretion of budesonide and its major, largely inactive metabolites, the PKs of budesonide are unlikely to be significantly affected by changes in renal function.

The elderly

PK data for budesonide in elderly individuals have not been presented separately.

Sex, ethnicity, genetic polymorphism)

There were no analyses of ethnicity or gender effects on the PKs of budesonide. Effects and consequences of genetic polymorphism have been discussed under above.

Pharmacokinetic interactions

Interactions demonstrated in human studies

No formal interaction studies were submitted.

Clinical implications of *in vitro* findings

It is known that metabolism of budesonide is primarily mediated though CYP450 3A. Furthermore, the pharmacokinetics of budesonide and its two major, inactive metabolites 16α-hydroxy-prednisolone and 6β-hydroxybudesonide in healthy volunteers are known to be influenced by intestinal CYP3A4 expression (Ufer 2008[36]). Therefore it can be reasonably expected that there is potential for potent CYP3A4 inhibitors such as ketoconazole to interact with Budenofalk, resulting in higher bioavailability and systemic exposure to budesonide. The possibility of PK interactions between budesonide and other drugs that are inhibitors, inducers or substrates of CYP3A is stated in the proposed draft PI.

Evaluator's overall conclusions on pharmacokinetics

The PKs of budesonide have previously been well described. Budesonide is known to display linear pharmacokinetics and is rapidly and almost completely absorbed after oral administration but has poor systemic availability (about 10%) due to extensive first-pass metabolism in the liver, mainly by the cytochome P450 isoenzyme CYP3A4. Its two major, inactive metabolites 16α-hydroxy-prednisolone and 6β-hydroxybudesonide have less than 1% of the glucocorticoid activity of unchanged budesonide.

The focus of the PK data submitted with the current application was to examine the PK profile of budesonide following its administration as a pH-controlled release formulation, including the effects of food; and to elucidate the PK profile in adult and paediatric patients with Crohn's

disease. Additionally, the effect of hepatic impairment has been further elucidated in patients with primary biliary cirrhosis.

The PK data were generated over an extended period spanning 1992 to mid-2006, using a variety of analytical methods. Some concern exists over whether there was interference with the assay from either endogenous or other exogenous compounds in the early studies that employed an HPLC/RIA assay (Studies BUC-5.C3 and BUC-5.C9/BIO & BUC-5.C18/BIO), indicated by the presence of baseline serum budesonide concentrations even before the drug was started. Otherwise, the PK data demonstrate that absorption of budesonide from Budenofalk capsules occurs with a lag time of approximately 2 to 3 h in healthy subjects, consistent with the pH-dependent delayed-release characteristics of the pellets within the capsules. A once daily and tid dosing regimen yielded similar PK parameters and bioavailability estimates except for differences in peak levels of budesonide which are elevated with the higher single dose as could be expected from the known linear pharmacokinetics. The oral bioavailability of a daily dose of 9 mg budesonide was consistently about 10-15% across the studies and there was no evidence of budesonide accumulation with repeated administration.

Considerable inter- and intra-individual variability in PKs of budesonide and its two major metabolites, 16α-hydroxy-prednisolone and 6β-hydroxybudesonide, were observed in studies of healthy volunteers and patients with Crohn's disease. There were no clinically relevant differences in PK parameters of budesonide for a 3 mg tid regimen between healthy subjects and adult patients with Crohn's disease at steady-state.

Administration of single doses of 3 mg and 9 mg Budenofalk with food was associated with prolongation of the lag time for appearance of budesonide in the systemic circulation by several hours, which is consistent with the effect of food delaying the passage of the budesonide pellets from the stomach into the duodenum. Correspondingly, t_{max} was also increased. The impact of food on PK parameters appeared to be greatest with a single 3 mg dose, for which the budesonide AUC was significantly decreased and clearance significantly increased with a trend toward a decrease in C_{max} was well. Similar but less marked (and statistically non significant) effects were observed for the effects of food on a single 9 mg dose of Budenofalk, with a small and clinically insignificant reduction of the estimated bioavailability from 15% to 12%. Due to the prolonged time delay in the release of budesonide if Budenofalk is taken together with a meal, the sponsor has recommended that Budenofalk should be taken half an h before meals. This appears reasonable.

The overall PK profile for paediatric patients was similar to that observed in adult patients. However, within the paediatric population, peak plasma concentrations of budesonide and its metabolites were higher in children (aged <12 years) than in adolescents (aged ≥12 years), with a less pronounced difference in AUCs unadjusted for weight. On a per kg basis, children had lower clearance and a smaller volume of distribution than adolescents. The PKs of repeated oral administration of 9 mg per day were similar to those after single dose administration both in children and in adolescents.

Severe hepatic impairment was shown to result in markedly elevated budesonide levels associated with the potential for serious ADRs.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 32 summarises studies relating to each pharmacodynamic topic summary.

Table 32. Submitted pharmacodynamic data.

PD Topic	Subtopic	Study ID*
Primary Pharmacology	Effect on inflammatory mediators in bowel mucosa	Nil studies
Secondary Pharmacology	Effect on serum cortisol incl. ACTH stim.	
	Adults	BUC-16/CDA
	Effect on serum cortisol	
	Adults	BUC-15/CDA
		BUC-5.C3 NBF_BF*
		BUC-5.C9 NBF_BF*
		Lundin et al 2003^*
		Hempfling et al 2003*
		Kolkman et al 2004
	Effect on serum osteocalcin	BUC-16/CDA
		BUC-23
	Effect on granulocytes/lymphocytes	BUC-5.C9/BIO & BUC-5.C18/BIO*
		BUC-14/BIO*
		BUC-5.C3*
		BUC-5.C3 NBF_BF*
		BUC-5.C9 NBF_BF*
		Kolkman et al 2004
Genetic, Gender and Age-Related Differences in PD Response	Effect of gender	Nil studies
	Effect of age	
	Effect of CYP3A polymorphism	BUC-59/BIO Ufer et al 2008
PD Interactions		Nil studies
Population PD and PK-PD analyses	Healthy subjects	Nil studies

PD Topic	Subtopic	Study ID*
	Target population	Nil studies

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ^ Studies conducted using Entocort

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Summary of capsule pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

Mechanism of action

The mechanism of action of budesonide, and corticosteroids more generally, has been the subject of extensive *in vitro* and *in vivo* pharmacology studies over many years. The information below is a summary of the sponsor's review of the published scientific literature.

The activity of glucocorticoids is mediated by specific cytoplasmic glucocorticoid receptors expressed in virtually all cells. Binding of glucocorticoids to the glucocorticoid receptor and the formation of a receptor complex is a prerequisite for their pharmacological and therapeutic action. Budesonide binds with high affinity to human and rat glucocorticoid receptors with a relative affinity 8-9 times higher than that of dexamethasone. Glucocorticoids are taken up into cells by passive diffusion into the cytoplasm where they bind to intracellular glucocorticoid receptors to form a complex, which enters the nucleus. The steroid-glucocorticoid receptor complex binds to glucocorticoid response elements, which induce gene transcription resulting in synthesis of several proteins including anti-inflammatory proteins (direct genomic regulation). The steroid-glucocorticoid receptor complex also interacts with other transcription factors such as the nuclear factor κB (NF-κB), resulting in inhibition of synthesis of inflammatory proteins (indirect genomic regulation). The non genomic pathways involve signalling though membrane associated receptors and second messengers. Glucocorticoids and the glucocorticoid receptor control a complex anti-inflammatory network. The *in vitro* anti-inflammatory activity of glucocorticoids and budesonide involves many different inflammatory cells and mediators. The cell types influenced by budesonide include lymphocytes, monocytes/macrophages, eosinophls, basophils/mast cells, neutrophils and endothelial cells. Budesonide influences activation, proliferation, growth and differentiation, migration, apoptosis, adhesion molecule expression, cytokine production and release of other inflammatory mediators.

Pharmacodynamic effects

Primary pharmacodynamic effects

No human data were presented concerning the primary pharmacodynamic effect of budesonide which, for the purpose of this submission, is considered to be its anti-inflammatory activity in the intestinal wall.

Secondary pharmacodynamic effects

As glucocorticoid receptors are expressed in virtually all cells, the pleiotropic effects of glucocorticoid receptors on multiple signalling pathways are responsible for the unwanted systemic side effects associated with glucocorticoid therapy. In addition to the anti-inflammatory activity, glucocorticoid effects include gluconeogenesis, proteolysis and lipolysis and adverse bone metabolism effects (osteoporosis and osteonecrosis) amongst others. Some glucocorticosteroids also have mineralocorticoid effects such as sodium and water retention

and potassium loss. Furthermore, the HPA axis plays a central role in regulating glucocorticoid receptor signalling though the endogenous natural glucocorticoid, hydrocortisone. Exogenous corticosteroids exert negative feedback on the HPA axis, resulting in decreased ACTH and adrenal suppression, reflected in decreased cortisol levels, particularly with repeated high doses. This manifests as an inability to mount suitable responses to stresses such as infection and trauma.

In the sponsor's submission, three measures of systemic pharmacodynamic effect with Budenofalk oral capsules were employed in the studies submitted for review; effect on serum cortisol levels (including response to ACTH stimulation), serum osteocalcin levels and lymphocyte and granulocyte counts.

Effects on serum cortisol levels as a measure of HPA axis suppression

Healthy volunteers

In 12 healthy volunteers a single 3 mg dose of Budenofalk reduced the cumulative 24 h cortisol levels (AUC) by 29% in the fed state (p=0.002) and 19% in the fasted state (p=0.063) compared to placebo (historical control) data from Study BUC-5.Placebo which was not submitted for evaluation (BUC-5.C3 NBF_BF). In Study BUC-5.C9 NBF_BF, a 9 mg Budenofalk dose reduced the cumulative 24 h cortisol levels in another 12 healthy volunteers by 41% in the fed state and 44% in the fasted state compared to placebo (p values not reported). These studies point indirectly to a dose response relationship. The effect of food was not statistically significant in either study.

Patient groups

Adults

A dose response relationship for suppression of plasma cortisol in adult patients with Crohn's disease was best demonstrated in the dose-ranging Study BUC-16/CDA. In this study patients received daily doses of either 3 mg budesonide (1 x 1 mg Budenofalk tid; n= 104), 9 mg budesonide (1 x 3 mg Budenofalk tid; n=104), 18 mg budesonide (2 x 3 mg Budenofalk tid; n=99) or placebo (n=102) for 56 days, followed by a dose reduction period during which patients in the 9 mg and 18 mg budesonide treatment groups received a daily dose of 6 mg budesonide (2 x 1 mg Budenofalk tid) and patients in the 3 mg budesonide and placebo groups received placebo for 14 days. Plasma cortisol levels were assessed at baseline and Days 14, 56 and 70. Additionally, corticotropin stimulation test results were available for 215 patients at baseline and for 188 patients at Day 56. The key findings were:

- a clear dose-response relationship for suppression of plasma cortisol by budesonide was evident by the first scheduled visit on study medication at Day 14 (Figure 14);
- at Days 14 and 56 the geometric mean ratio to baseline was statistically significantly different for both budesonide 9 mg and 18 mg compared to placebo ($p < 0.001$ for each group);
- by Day 70 (following dose reduction in the 9 and 18 mg groups and withdrawal in the 3 mg group from Day 56) plasma cortisol levels had improved towards baseline values in all the budesonide groups;
- the number of patients with an impaired response to corticotropin stimulation increased in all 3 budesonide treatment groups during treatment; increases of 17% in the 3 mg group, 43% in the 9 mg group and 55% in the 18 mg group, whilst the rate in the placebo group remained stable (Table 33). The changes from baseline at Day 56 were significantly different compared to placebo for both the budesonide 9 mg and 18 mg treatment groups ($p \leq 0.001$) but not the 3 mg treatment group (p=0.053); and

- of note, a significant proportion of patients in all groups (ranging from 33-46%) had impaired responses at baseline, possibly indicating carry over effects from previous steroid treatment.

In another dose ranging study that was not placebo controlled (BUC-15/CDA), a dose response relationship was also observed in patients who received daily doses of either 6 mg budesonide (2 x 1 mg Budenofalk tid; n= 105), 9 mg budesonide (1 x 3 mg Budenofalk tid; n=99) or 18 mg budesonide (2 x 3 mg Budenofalk tid; n=106) for 12 to 15 weeks. The initial plasma cortisol levels did not differ between the groups but at all follow-up visits the mean and median plasma cortisol levels in patients given 18 mg budesonide daily were lower than those of patients given 9 mg budesonide daily which were in turn below those of the patients given 6 mg budesonide daily.

Figure 14. Geometric mean plasma cortisol by visit and treatment group (BUC-16/CDA)

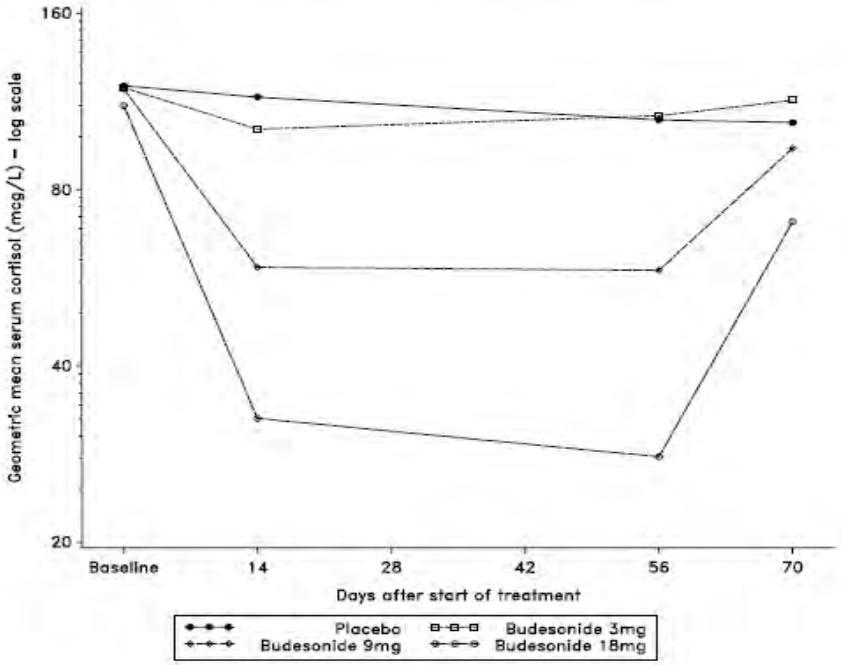


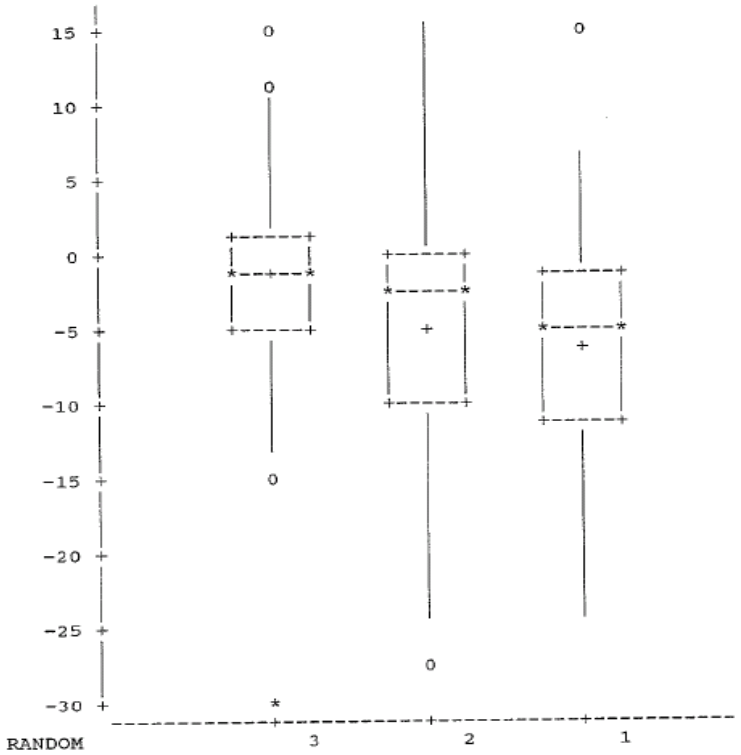
Table 33. Proportion of patients with impaired response to corticotropin stimulation (BUC-16/CDA)

	Treatment Groups			
	placebo	budesonide 3 mg	budesonide 9 mg	budesonide 18 mg
Baseline	n = 54	n = 57	n = 55	n = 49
Impaired Response	22 (41%)	26 (46%) p=0.745	25 (45%) p=0.762	16 (33%) p=0.519
Day 56	n = 48	n = 49	n = 49	n = 42
Impaired Response	20 (42%)	31 (63%) p=0.053	43 (88%) p=< 0.001	37 (88%) p=< 0.001

Changes in plasma cortisol concentrations from baseline to the end of individual therapy increased with increasing daily dose (Figure 15) with significant differences between the treatment groups (6 mg versus 9 mg daily p = 0.0484; 9 mg versus 18 mg, p = 0.0001; and 6 mg versus 18 mg, p = 0.0001). In this study patients were also stratified according to whether they had (Stratum 2) or hadn't (Stratum 1) received treatment with a systemically acting glucocorticosteroid in the 2 weeks prior to the initial visit. Patients in Stratum 2 were switched to Budenofalk according to a specified reduction scheme during the first part of the trial and depending on the previous corticosteroid the overlapping treatment phase lasted up 3 weeks. Not surprisingly, the plasma cortisol concentrations were lower in that stratum at the initial

visit, however a dose response was still observed with respect to the change from baseline to the end of individual therapy (Table 34).

Figure 15. Box and whisker plots of the change in plasma cortisol at end of therapy from the initial visit (all patients study BUC-15/CDA)



3 = 3 x 2mg Budenofalk 2 = 3 x 3mg Budenofalk 1 = 3 x 6mg Budenofalk

Table 34. Plasma cortisol concentration (µg/dl) by stratum (BUC-15/CDA)

Intention to treat	3x2 mg budesonide		3x3 mg budesonide		3x6 mg budesonide	
	Stratum 1	Stratum 2	Stratum 1	Stratum 2	Stratum 1	Stratum 2
Initial Visit:						
mean	14.3	9.8	18.9	10.1	13.8	9.9
S.D.	5.8	6.8	8.6	7.0	6.5	6.4
min.	4.1	1.9	1.9	1.9	4.7	1.9
median	14.0	8.8	18.5	9.4	13.0	8.8
max.	32.0	26.0	40.0	29.0	38.0	27.0
valid n	39	62	32	61	32	72
Individual end of treatment*:						
mean	11.2	8.9	9.7	7.4	5.6	4.6
S.D.	7.0	6.1	7.7	5.4	6.7	4.8
min.	1.9	1.9	1.9	1.9	1.9	1.9
median	11.0	7.8	10.5	5.9	1.9	1.9
max.	34.0	32.0	35.0	27.0	35.0	26.0
valid n	36	63	29	65	31	72

Evaluator's comment

Each of the dose ranging studies used a 1 mg Budenofalk capsule to achieve daily doses of 3 mg and 6 mg budesonide respectively. The 1 mg strength is not intended for marketing. No pharmacokinetic or pharmaceutical chemistry data were presented to support the use of the 1 mg strength in these studies.

Also of note, the introduction to Study BUC-16/CDA referred to a Phase I study in healthy volunteers that reportedly showed Budenofalk to have a dose dependent effect (the actual PD parameters were not specified) when administered orally as 1 mg, 2 mg and 3 mg capsules. The systemic duration of action (once again the actual PD parameters were not specified) after a single dose of 2 mg Budenofalk was stated to be 8 h. It was also stated that the duration of activity has also been shown to be approximately 8 h in patients with an ileostomy. The references cited in support of these statements were all poster abstracts. These data have not been submitted with the current submission.

In the pivotal confirmatory efficacy Study BUC-52/CDA, mean cortisol (± SD) levels decreased during 8 weeks of treatment with budesonide 3 mg tid (3.97 ± 5.65 µg/dL) and budesonide 9 mg od (5.05 ± 7.98 µg/dL), whilst they remained stable in a mesalazine comparator group. The reductions were slightly greater in the budesonide groups when only morning cortisol measurements were analysed (4.65 ± 5.68 µg/dL for BUC 3 mg tid; 6.01 ± 7.76 µg/dL for BUC 9 mg od). The proportions of patients with a shift from normal cortisol levels at baseline to levels below the normal range (5 to 25 µg/dL) were 2% for mesalazine, 29% for budesonide 3 mg tid and 31% for budesonide 9 mg od group. This mirrored the changes in the mean values. Decreased serum cortisol levels were recorded as an adverse event in 5.1% of patients receiving the 3 mg tid regimen and 3.9% of patients receiving the 9 mg od regimen.

Suppression of plasma cortisol levels was also observed in 15 patients with acute left-sided ulcerative colitis after 9 mg Budenofalk daily for 5 days (Kolkman et al 2004/BUC-18). The degree of suppression was more pronounced with a 9 mg once daily regimen (n=7) than with a 3 mg tid regimen (n=8).

Areas under the 24 h plasma cortisol concentration-time curves were decreased in patients with both mild/moderate hepatic impairment (early stage Primary Biliary Cirrhosis (PBC); n=12) and more severe hepatic impairment (late stage PBC; n=7), with much greater effect in patients observed with more severe impairment (Hempfling et al 2003[38]). In this study doses of budesonide were escalated from 3 mg daily to 3 mg tid over 21 days. Suppression of cortisol levels was observed as early as Day 7 (after doses of 3 mg od) in patients with severe hepatic impairment, whereas in patients with mild/moderate impairment significant suppression was first observed at 21 days (after full dose escalation, including 3 mg tid for the last 5 days). Similar effects were observed with respect to trough plasma cortisol concentrations and 24 h urinary cortisol excretion.

Effect on bone metabolism

Healthy volunteers

Not assessed.

Patient groups

The effects of Budenofalk on bone metabolism were assessed by measuring serum osteocalcin levels at baseline and after 8 weeks treatment in 250 adult patients with Crohn's disease who participated in the placebo controlled dose finding Study BUC-16/CDA. The change from baseline at Day 56 was compared across the different treatment groups using analysis of variance adjusted for centre and treatment effects and with the baseline value as a covariate. Serum osteocalcin levels decreased in all the budesonide groups in a dose related manner (Table 37). Only for budesonide 18 mg was the difference compared to placebo statistically significant (p=0.002).

Table 37. Effect of Budenofalk (0, 3, 9 and 18 mg) given for 8 weeks on serum osteocalcin levels in adults with Crohn's disease (BUC-16/CDA)

	Placebo	Budesonide 3mg	Budesonide 9mg	Budesonide 18mg
Baseline				
n	51	54	52	52
Mean	6.7	6.9	6.8	6.3
SD	4.71	4.04	4.42	3.79
Median	5.4	6.4	6.1	5.4
Day 56				
n	51	61	53	54
Mean	7.3	6.6	6.6	5.0
SD	4.76	3.60	5.16	3.28
Median	6.8	6.4	5.6	4.6
Change from baseline at day 56				
n	42	49	43	44
Mean	0.8	-0.1	-0.8	-1.4
SD	3.85	4.07	5.75	3.47
Median	0.8	-0.4	-1.0	-1.0
Difference from placebo		-0.3	-0.7	-2.4
95% CI		-1.8 to 1.1	-2.2 to 0.8	-3.9 to -0.9
p value		0.657	0.381	0.002

In the confirmatory pivotal study in adults (BUC-23), neither Budenofalk 3 mg tid for 8 weeks nor prednisone 40 mg daily tapering to 5 mg daily over 8 weeks had any clinically significant effect on serum osteocalcin levels. In the Budenofalk group the mean osteocalcin level reduced slightly from 9.2 ± 3.6 ng/mL at baseline to 8.5 ± 2.9 ng/mL at Visit 5 (LOCF). Osteocalcin levels were unchanged in the prednisone group (baseline: 9.6 ± 5.2 ng/mL, Visit 5 (LOCF): 9.6 ± 4.5 ng/mL).

Pharmacodynamic effects on bone growth and metabolism were not assessed in paediatric patients.

Effect on peripheral blood lymphocyte and granulocyte counts

Healthy volunteers

The effect of Budenofalk on granulocyte and lymphocyte counts over 24 h in healthy volunteers was assessed for:

- single doses of 9 mg and 18 mg (BUC-5.C9/BIO & BUC-5.C18/BIO);
- 3 mg given at 8 hourly intervals (BUC-5.C3); and
- single doses of 3 mg and 9 mg administered in both fed and fasted states (BUC-5.C3 NBF_BF and BUC-5.C9 NBF_BF, respectively).

These results are summarised in Table 38. Study BUC-5.C9/BIO and BUC-5.C18/BIO employed a parallel group design and although the differences in effects of the two doses on lymphocyte and neutrophil counts were not statistically significant, there was a trend toward increasing effect with increasing dose. Indirect comparison of the effects of 9 mg daily given as a single dose (BUC-5.C9) versus divided (tid) dose (BUC-5.C3) suggests a greater effect from the once daily dose regimen, however, this unlikely to be clinically relevant.

The impact of food on the PD effects of Budenofalk was studied in 2 cross over studies that found that fasting before a 3 mg dose was associated with a statistically significantly higher degree of lymphocyte suppression and granulocyte elevation, which is consistent with the higher bioavailability and AUC for budesonide observed in the fasting state (BUC-5.C3 NBF_BF; n=12). The food effect was not as marked with the 9 mg dose (BUC-5.C9 NBF_BF; n=12).

Table 38. Effect of Budenofalk on lymphocytes & granulocytes by in healthy subjects

	BUC-5.C3 NBF_BF		**BUC-5.C3**	**BUC-5.C9 NBF_BF**		**BUC-5.C9/BIO BUC-5.C18/BIO**	
	3mg fed	**3mg fasted**	**3mg tid**	**9mg fed**	**9mg fasted**	**9mg**	**18mg**
n	12	12	12	12	11	8	6
Lymphocytes							
Change in $AUC_{0\text{-}24}$ (%hr)*			278 ± 284			329 ± 321	375 ± 310
% Suppression from baseline*	6 ± 9	15 ± 10		17 ± 10	19 ± 14		
Time to peak (hrs)	6-8	6-8	6-8	7-8	7-8	10	10
Neutrophils							
Change in $AUC_{0\text{-}24}$ (%hr)*			-314 ± 244			-259 ± 216	-430 ± 394
% Suppression from baseline*	-5 ± 7	-14 ± 9		-13 ± 10	-16 ± 11		
Time to peak (hrs)	6-8	6-8	6-8	7-8	7-8	10	10

* positive value represents a decrease and a negative value an increase, for neutrophils, %hr (an increase) with the 9mg dose and %hr with the 18mg dose.

Patients

Changes in lymphocyte and granulocyte counts observed over a 24 h period at steady state in patients with Crohn's disease (BUC-14/BIO) and left sided ulcerative colitis (Kolkman et al 2004[37]; BUC-18) are shown in Figures 16 and 17.

In Study BUC-14/BIO the cumulative effects on granulocytes and lymphocytes were not pronounced. At steady state there was an increase in the lymphocyte AUC over 24 h, which is counter to that observed in studies of Budenofalk in healthy volunteers. In addition, the increase in neutrophil AUC was much lower than that observed for the same regimen administered *de novo* to healthy volunteers (BUC-5.C3). However, true baseline values were not available for either parameter. Of note, lymphocyte baseline values from healthy volunteers (mean value: 39% of total white blood cells) and zero values from this study (24% of total blood white cells) were highly significantly different.

Figure 16. Effect of Budenofalk on lymphocytes and neutrophils at steady state in adult patients with Crohn's disease (BUC-14/BIO)

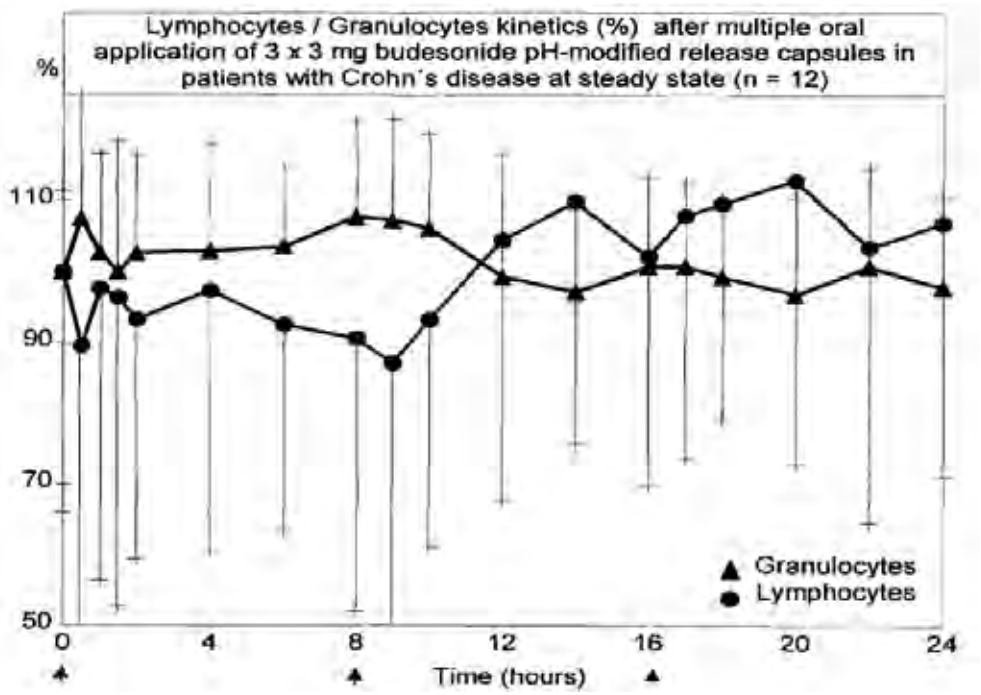
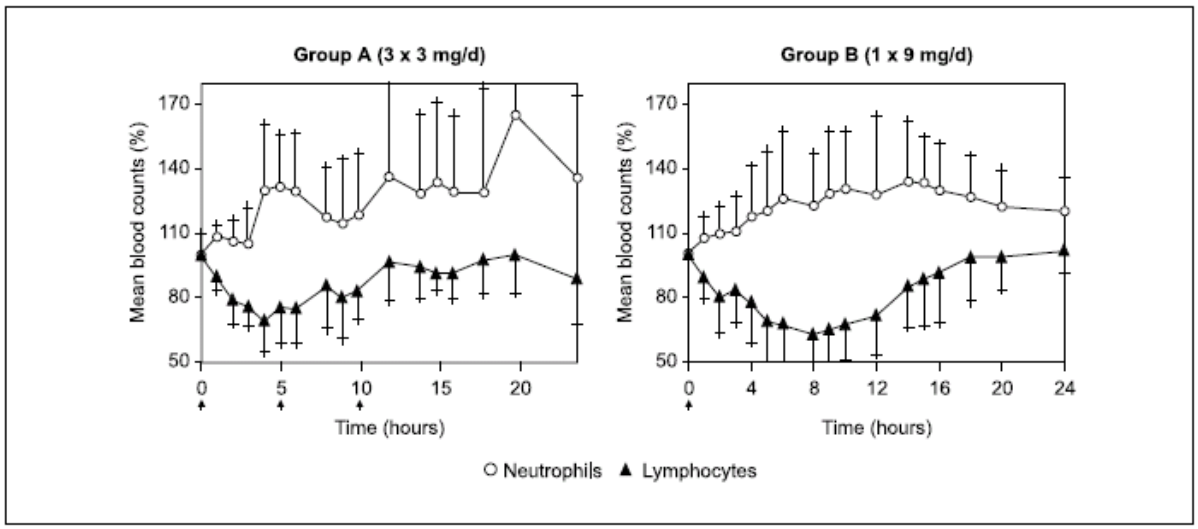


Figure 17. Effect of Budenofalk on lymphocytes and neutrophils at steady state in adult patients with ulcerative colitis (Kolkman et al 2004)



In the study by Kolkman et al 2004[37], administration of 9 mg budesonide as single undivided dose resulted in a much greater increase in neutrophils over 24 h than observed for the same regimen in healthy volunteers (BUC-5.C9 NBF_BF), whilst the effects on lymphocytes were comparable.

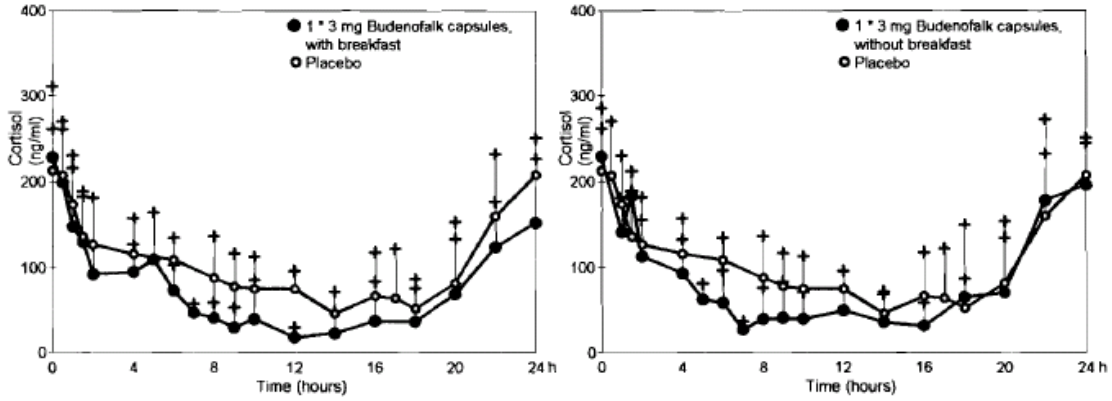
Additionally, Hempfling et al 2003[38] (BUC-39) reported there were no significant changes in lymphocyte and neutrophil counts in patients with hepatic impairment but this could not be evaluated further as no actual data were presented.

Interpretation of the effects of Budenofalk on lymphocyte and neutrophil counts in these studies in patients is problematic because the studies were conducted at steady state and so the changes in cell counts essentially reflect changes about the zero time value which would have been already affected by systemic exposure to budesonide and also because of confounding by the patients' disease states.

Time course of pharmacodynamic effects

Endogenous cortisol levels were monitored for 24 h following a single 3 mg dose of Budenofalk in Study BUC-5.C3. Only the cumulative 24 h results were discussed within the text of the report and these are presented in the PD section of this CER. However, it is evident from a graphical presentation of data from within the study report (reproduced as Figure 18) that the maximal effect on plasma cortisol (compared to placebo) was approximately 7 h in the fasting state and at 12 and 24 h in the fed state.

Figure 18. Time course of effect of a single 3mg dose of Budenofalk on mean ± SD cortisol levels in the fed and fasting state (BUC-5.C3 NBF_BF). (Placebo data are shown for comparison)



With repeated dosing, a clear dose response relationship for suppression of plasma cortisol by budesonide was evident by the first scheduled visit on Day 14.

Peak effects on lymphocyte and granulocyte counts (as a percentage of total White Cell Count (WCC)) following administration of a single dose of Budenofalk to healthy volunteers in the fasting state, were observed at between 6-8 h (BUC-5.C3) and 10 h post administration (BUC-5.C9/BIO and BUC-5.C18/BIO). The administration of food prolonged the peak effect from 7-8 h to 10-12 h in Study BUC-5.C9 NBF_BF, whereas it appeared to have very minimal effect in Study BUC-5.C3 NBF_BF.

Relationship between drug concentration and pharmacodynamic effects

Integrated PK/PD analyses correlating the serum concentrations of budesonide with its pharmacodynamic effects on lymphocyte and granulocyte counts were performed in Studies BUC-5.C3, BUC-5.C9/BIO and BUC-5.C18/BIO. These analyses, of 3 x 3 mg, 1 x 9 mg, 1 x 18 mg doses of Budenofalk suggested there was no dependency of pharmacodynamic parameters on the dose.

Genetic-, gender- and age-related differences in pharmacodynamic response

There were no data examining genetic or gender related differences in pharmacodynamic response. Effects of Budenofalk on plasma cortisol levels and responses to ACTH stimulation were examined in children and adolescents in Studies BUC-47/CDA, BUC-48/BIO and Levine et al 2003[55]. Additional data generated for Entocort capsules were reported by Lundin et al 2003[81] and Escher et al 2004[57]. All these studies were conducted at steady state, thus the time course of the PD effects could not be examined.

Pharmacodynamic interactions

No studies investigating potential pharmacodynamic drug interactions with budesonide were submitted. The sponsor stated that, as the broad clinical experience with budesonide had shown no evidence for a specific pharmacodynamic interaction of budesonide with other compounds, conduct of specific interaction studies were deemed not necessary. This seemed reasonable.

Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamic profile of budesonide has been extensively studied previously in relation to its clinical applications in asthma (for example with Pulmicort Turbuhaler) and IBD (for example, Entocort). Thee measures of systemic pharmacodynamic effects of Budenofalk oral capsules were employed in the studies submitted for review; effect on serum cortisol levels

(including response to ACTH stimulation), serum osteocalcin levels, and lymphocyte and granulocyte counts

The effects of Budenofalk pH controlled release capsules on plasma cortisol levels were evaluated in clinical pharmacology studies with budesonide in healthy adult subjects and in patients with Crohn's disease (adult and paediatric) and distal ulcerative colitis (adults) and adults with hepatic impairment. Decreases in mean plasma cortisol levels were observed at all doses of budesonide tested (3 mg, 6 mg, 9 mg and 18 mg) in both healthy volunteers and patients with a clear dose-response relationship for both suppression of cortisol levels and impairment of response to ACTH stimulation having been demonstrated in adult Crohn's disease patients. There was also evidence that a 9 mg once daily dose was associated with slightly higher suppression of cortisol levels than a 3 mg tid regimen. Food did not have an impact the degree of suppression of cumulative 24 h cortisol levels in healthy volunteers.

Budenofalk had a small dose related effect on serum osteocalcin levels during the short-term (8 weeks) treatment of adult patients with Crohn's disease. Pharmacodynamic effects on bone growth and metabolism were not assessed in paediatric patients.

Budenofalk has only a small effect on lymphocytes and granulocytes in healthy subjects or patients when administered as 3 mg TID or 9 mg od.

Integrated PK/PD analyses of the data correlating the serum concentrations of budesonide with its pharmacodynamic effects on lymphocytes and granulocytes at single doses of 3 x 3 mg, 1 x 9 mg or 1 x 18 mg of Budenofalk suggested there was no dependency of pharmacodynamic parameters on the dose.

Dosage selection for the pivotal studies

Confirmatory studies in adult Crohn's disease

The pivotal confirmatory studies submitted for the indication of induction of remission in adult Crohn's disease were BUC-52/CDA, in which the efficacy and safety of Budenofalk given in either 9 mg once daily regimen or a 3 mg tid regimen was compared with mesalazine 4.5g daily over a treatment period of 8 weeks, and BUC-23, in which the efficacy and safety of Budenofalk 3 mg tid was compared with a tapering dose of prednisone over an 8 week period.

The choice of the Budenofalk dosage regimens for Study BUC-52/CDA, being the last confirmatory study to have been commenced and completed (November 2004 to May 2008) was based on the accumulated evidence from the exploratory studies by Caesar et al 1997[41] and Gross et al, 1996[40] and an earlier confirmatory study (BUC-23). These studies involving patients with active Crohn's disease of the ileum and/or ascending colon showed that treatment with Budenofalk 3 mg tid over similar periods of time yielded remission rates of 50-60%. The secondary objective of comparing Budenofalk given as a 9 mg od or 3 mg tid regimen in Sstudy BUC-52/CDA was based on literature reports that Entocort 9 mg od was as effective as 4.5 mg bdin the treatment of adult Crohn's disease (Campieri et al 1997[45]; Tremaine et al 2002[43]). This study was conducted at a time when the PK/PD development program in adults was essentially completed (except for Study BUC-59/BIO), which together with the dose-finding Study BUC-15/CDA had demonstrated the clear dose related effects of Budenofalk.

Study BUC-23 was planned and conducted some years earlier (July 1995 to January 1997) and the choice of a 3 mg tid regimen was at that time based on the exploratory study by Gross et al., 1996[40] that suggested that budesonide had a similar success rate but fewer accompanying side effects than standard therapy with prednisone as well as results reported for Entocort 9 mg/day

in the published literature (Wolman and Greenberg, 1991[86]; Löfberg et al. 1993[49], Greenberg et al. 1994[42]; Rutgeerts et al. 1994[24] and Roth et al.1993[87]).

Two dose finding studies (BUC-15 CDA and BUC-16/CDA) were also conducted during the development program. Study BUC-15/CDA was conducted from October 1994 to November 1995 because (with the exception of a paper by the Canadian Inflammatory Bowel Disease Study Group, 1993) to that time no dose finding study had been undertaken with budesonide. Study BUC-16/CDA was undertaken (from August 1995 to August 1997) to confirm the experience gained from previous studies that 9 mg budesonide daily was the optimum dose in Crohn's disease. Doses of 3 mg daily had been found to produce increased remission rates but not significantly better than placebo and a comparison of 15 mg and 9 mg doses of budesonide (given as Entocort), also undertaken by the Canadian Inflammatory Bowel Disease Study Group, had shown no significant difference between the two dose regimens (Greenberg et al, 1994[42]). In addition, experience from compassionate use of budesonide suggested that a dose of 18 mg produced a more rapid response to treatment. The conduct of this study in the Soviet Union provided an opportunity to compare doses of 3 mg, 9 mg and 18 mg budesonide with placebo to determine the lowest effective dose of Budenofalk. However, this study failed to demonstrate a dose response for its primary and secondary efficacy outcomes.

Efficacy

Adult Crohn's disease

Four exploratory studies (BUC-15/CDA, Gross et al 1996, Caesar et al 1997[41] and BUC-16/CDA) and two confirmatory studies (BUC-23 and BUC-52/CDA) all using Budenofalk oral capsule, were submitted in support of the indication for the induction of remission in adult Crohn's disease patients. Of these 6 studies, 4 formed the basis for the original approval in other jurisdictions (BUC-23, BUC-15/CDA, Gross et al 1996[40] and Caesar et al 1997[41]).

Confirmatory (Pivotal) efficacy studies

Study BUC-52/CDA

Study design, objectives, locations and dates

This Phase III, randomised, double blind, double dummy, multicentre study compared the efficacy and safety of 9 mg daily Budenofalk oral capsules (BUC) and 4.5 g daily Salofalk oral mesalazine tablets (Dr Falk Pharma GmbH) in moderately active Crohn's disease. The study was conducted from November 2004 to May 2008 at 46 sites; 6 in Germany, 2 in Greece, 6 in Hungary, 9 in Israel, 5 in the Slovak Republic, 5 in Croatia and 13 in the Czech Republic.

Inclusion and exclusion criteria

Patients 18 to 70 years of age with Crohn´s disease of at least 3 month's standing, confirmed by endoscopic and histological, or endoscopic and radiological criteria and localised to either the terminal ileum, ascending colon or ileocolitis with a currently active disease (CDAI between 200 and 400) were eligible for study entry. Patients with macroscopic Crohn's lesions of the upper gastrointestinal tract or symptomatic stenosis and those known to be steroid-refractory or steroid dependent from previous active episodes were excluded. Also, patients requiring concomitant or recent treatment with conventional IV, PO or rectal steroids (within the last 2

[86] Wolman S L, Greenberg G R. Oral Budesonide in active Crohn´s disease: an initial experience. *Gastroenterology* 1991; **100**: A263.

[87] Roth M, Gross V, Schölmerich J, et al. Treatment of active Crohn's disease with an oral slow-release budesonide formulation. *Am J Gastroenterol* 1993; **88(6)**: 968-9.

weeks); > 6 mg/day budesonide PO or > 3 g/d mesalazine PO (2 weeks); ketoconazole, ciprofloxacin or other CYP3A inhibitors (1 month); immunosuppressive agents, cytostatics, methotrexate, or cyclosporine (3 months); or anti-TNF-α therapy (6 months) before the baseline visit were excluded. Patients were allowed to have received azathioprine or 6-MP for maintenance of remission only and only if the dose was unchanged within the last 3 months before baseline visit and during the study. Other exclusion criteria were gastrointestinal infection, diabetes mellitus, cancer, clinically significant cardiac disease, disturbances of hepatic and renal function, pregnancy and lactation.

Study treatments

Patients were randomised to receive treatment for 8 weeks with either:

- Budenofalk 3 mg capsules: 1 x 3 mg tid
- Budenofalk 3 mg capsules: 3 x 3 mg od
- Salofalk (mesalazine) 500 mg tablets: 3 x 500 mg tid

Efficacy variables and outcomes

The main efficacy variable was the CDAI.

The primary efficacy outcome was clinical remission, where remission was defined as CDAI ≤ 150 at final (Week 8)/withdrawal visit. If a patient discontinued the study prematurely, the last value on study medication was considered. If no follow-up CDAI under study medication was documented, no achievement of remission was assumed. For patients without a documented CDAI at the final examination, the last CDAI recorded under study medication was used (LOCF).

Other efficacy outcomes included:

- Clinical remission (CDAI ≤ 150) for BUC 3 mg tid versus BUC 9 mg od
- Response (70), defined as CDAI ≤ 150 or reduction of at least 70 points in CDAI
- Response (100), defined as CDAI ≤ 150 or reduction of at least 100 points in CDAI
- Time to remission: time from baseline to the day when CDAI was ≤ 150 for the first time
- Time to response (70)
- Time to response (100)
- CDAI per visit and mean change from baseline CDAI
- Mean changes from baseline in ESR and CRP
- Quality of life: assessed using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

Sample size

The primary goal of the study was to show superiority of budesonide over mesalazine. A χ^2-test of superiority (one-sided test, $\alpha = 0.025$, normal approximation, no continuity correction) was planned. Based on published literature, it was expected that the remission rate for budesonide would be between 55% and 60% and the remission rate for mesalazine between 40% and 45%. Therefore, a clinically relevant difference in the remission rates of 15% was intended to be shown with 80% power.

An adaptive 3-stage group sequential design with optimal α spending was used, with the possibility for sample size adaptation at the first and second interim analysis. The study was originally designed as follows:

- in case of study continuation and without adaptation made at the two interim analyses, the planned sample size would have been 364 evaluable patients.

- the trial could be stopped or the sample size could be adapted at the interim analyses, in which case the total sample size could not be fixed. However, the sample size was estimated to be 362 patients on average under the null hypothesis and 286 patients on average under the alternative hypothesis.

Randomisation and blinding methods

Randomisation occurred in blocks of four using a centralised, computer-generated randomisation list. Blinding thoughout the study was achieved using the double dummy-technique, whereby all patients across the 3 groups took a combination of 14 active and placebo preparations (5 capsules and 9 tablets) per day while maintaining double-blindness as follows: 3 capsules and 3 tablets in the morning, 1 capsule and 3 tablets at noon and 1 capsule and 3 tablets in the evening. The placebo tablets and capsules were identical in size and appearance to their active counterparts.

Statistical methods

Up to two pre planned interim analyses were foreseen depending on the outcome of each interim analysis. The interim analyses were performed and assessed by an Independent Data Monitoring Committee (IDMC). The IDMC was composed and operated in adherence to pre defined rules as written down in a study specific standard operating procedures (SOP). Any modifications to the study conduct such as stop of recruitment, adaptation of sample sizes or switch of statistical hypotheses were recommended by an independent statistician who was a member of the IDMC.

At the first interim analysis, superiority of budesonide over mesalazine was not statistically significant and based on the observed remission rates at that stage (especially the mesalazine remission rate of 59%) the sample size for superiority testing was re estimated to require an additional 520 patients per group (1040 patients in total) to retain 80% power for the same between group difference. The IDMC recommended a switch from superiority to non-inferiority testing as planned in the protocol.

Consequently, the primary efficacy outcome was analysed using the χ^2-test for shifted hypotheses according to Farrington and Manning (one-sided test of non-inferiority, non-inferiority margin Δ=-0.10) with logistic regression for analysis of covariate effects.

Absolute and relative frequencies were calculated for the secondary remission and response rates with a χ^2-test (two-sided) and 95%CIs for difference in proportions. Time to response and remission were analysed using summary statistics and 95%CIs and time to event analysis (Kaplan-Meier curves), log rank test and generalised Wilcoxon test. Changes in CDAI, CRP, ESR and SIBDQ were analysed using summary statistics including 95%CIs and t-test.

Participant flow

A total of 311 patients were randomised to treatment; 81 to BUC 3 mg tid; 77 to BUC 9 mg od and 153 to mesalazine. Some 254 (82.2%) patients completed the study. Two patients randomised to budesonide 3 mg tid did not take any study medication, resulting in 309 evaluable patients in the safety population. One patient in the BUC 3 mg tid group and one in the 9 mg od group had no active Crohn's Disease at the start of the study and were excluded from the ITT analysis, giving a total ITT population of 307, comprising 78 patients in the BUC 3 mg tid group, 76 patients in the BUC 9 mg od group and 153 patients in the mesalazine group. Major protocol violations were found in 54 patients resulting in their exclusion from the PP analysis set as follows: 12 patients in the BUC 3 mg tid group, 8 in BUC 9 mg od group and 34 in the mesalazine group. The PP population thus comprised a total of 253 patients with 66 in the BUC 3 mg tid group, 68 patients in the group budesonide 9 mg od and 119 patients in the mesalazine group.

The number of patients per centre ranged from 1 to 44 at an average of 7 per centre and a median of 3, with 24 centres enrolling 3 or fewer patients and only 9 enrolling 10 or more patients.

Baseline data

The treatment groups were well matched at baseline with respect to demographic and key disease characteristics, including previous treatment of the current acute episode. There was an even balance of gender, the mean age was 37 years and all but 2 patients were Caucasian. The majority of patients (75%) were aged less than 40 years. The average time between the first diagnosis and study entry was 6 years.

Points of note:

- there were fewer patients with involvement of the distal colon in the mesalazine group than in the total BUC group. The two BUC groups did not differ remarkably in this regard;
- there were slightly more patients with extraintestinal manifestations in the total BUC group than in the mesalazine group. A notable difference in the presence of extraintestinal manifestations was also observed between the two BUC groups (proportion of patients with extraintestinal manifestations was 10.3% higher in the BUC 9 mg od group than in the 3 mg tid group);
- although there was no difference between the mean CDAI for the total BUC group and the mesalazine group at baseline, the proportion of patients with a CDAI > 300 at baseline was 4.7% higher in the mesalazine group than in the total budesonide group (25.5% versus 20.8%), with an even more marked difference between the two BUC groups (9 mg od 25.0% versus 3 mg tid 16.7%). A possible bias due to baseline differences of the CDAI was controlled by analysing change values instead of raw data;
- more patients in the BUC 9 mg od group than in the 3 mg tid group (63.2% versus 52.6%)had a disease duration of <5 years. All other demographic and baseline characteristics were comparable in the BUC groups; and
- similar findings were found for the PP population.

The duration of treatment with study medication ranged from 5 to 6l days in the BUC 3 mg tid group (mean ± SD: 52.5 ± l0 days); 4 to 62 days in the BUC 9 mg od group (52.2 ±10.4 days); and l to 66 days in the mesalazine group (48.2 ± 16.l days).

Results for the primary efficacy outcome

The proportions of patients with a CDAI ≤ 150 at final (Week 8)/withdrawal visit are summarised in Table 39 which shows that the ITT and PP remission rates were higher with Budenofalk treatment than mesalazine treatment (ITT: 69.48% versus 62.09%; between-group difference 7.39% [95%CI -3.19% to 17.97%], p=0.0013). The lower bounds of the 95% CIs for the difference in proportions well away from the non-inferiority margin of -10% for both the ITT and PP analyses, providing robust demonstration of the non-inferiority of budesonide compared to mesalazine.

Table 39. Overall clinical remission rates (LOCF) in confirmatory Study BUC-52/CDA

ITT analysis set	Budesonide 3 mg TID (n=78)	Budesonide 9 mg OD (n=76)	Total Budesonide (n=154)	Mesalazine 1.5 g TID (n=153)	Total (n=307)
Remission n (%) 95% CI	56 (71.79%) 61.81% to 81.78%	51 (67.11%) 56.54% to 77.67%	107 (69.48%) 62.21% to 76.75%	95 (62.09%) 54.40% to 69.78%	202 (65.80%) 60.49% to 71.10%
Difference in proportions (95% CI)	-4.69%[1] (-19.23% to 9.85%)		7.39%[2] (-3.19% to 17.97%)		
PP analysis set	**Budesonide 3 mg TID (n=66)**	**Budesonide 9 mg OD (n=68)**	**Total Budesonide (n=134)**	**Mesalazine 1.5 g TID (n=119)**	**Total (n=253)**
Remission n (%) 95% CI	50 (75.76%) 65.42% to 86.10%	47 (69.12%) 58.14% to 80.10%	97 (72.39%) 64.82% to 79.96%	82 (68.91%) 60.59% to 77.22%	179 (70.75%) 65.15% to 76.36%
Difference in proportions (95% CI)	-6.64%[1] (-21.72% to 8.44%)		3.48%[2] (-7.77% to 14.73%)		

Results for other efficacy outcomes

The results for the secondary variables are summarised in Table 40 which shows that responses to treatment [70/100], time to remission/response [70/100], CDAI change and the physician's global assessment were consistent with the primary efficacy outcome. CRP and ESR showed similar but small improvements on all treatments.

The SIBDQ showed small increases in all treatment groups (mean absolute change: 1.42 points for BUC 3 mg tid; 1.45 points for BUC 9 mg od; and 1.15 points for mesalazine1.5 g tid, with mean relative (%) changes from baseline of 47.25% for the total BUC group versus 37.51% for the mesalazine group).

There was no significant difference between the two BUC dosage regimens in remission rates (3 mg tid 71.8% versus 9 mg od 67.1%, p=0.5275). Both treatment regimens induced clinically significant reductions in CDAI scores (mean reductions from baseline to final visit (LOCF) of 149.9 and 147.7, respectively) and rates of response (100) were also very similar for the two regimens (76.9% versus 75.0%, respectively).

Table 40. Secondary efficacy outcomes in confirmatory Study BUC-52/CDA

Response (70/100) to treatment:

ITT analysis set		Budesonide 3 mg TID	Budesonide 9 mg OD	Total Budesonide	Mesalazine 1.5 g TID	Total
Response to treatment (70)	n/N (%)	64/78 (82.1%)	58/76 (76.3%)	122/154 (79.2%)	109/153 (71.2%)	231/307 (75.2%)
Response to treatment (100)	n/N (%)	60/78 (76.9%)	57/76 (75.0%)	117/154 (76.0%)	105/153 (68.6%)	222/307 (72.3%)

N: group total

Physician's global assessment:

ITT analysis set		Budesonide 3 mg TID	Budesonide 9 mg OD	Total Budesonide	Mesalazine 1.5 g TID	Total
Therapeutic success	n/N (%)	51/78 (65.4%)	45/76 (59.2%)	96/154 (62.3%)	80/153 (52.3%)	176/307 (57.3%)
Therapeutic benefit	n/N (%)	69/78 (88.5%)	68/76 (89.5%)	137/154 (89.0%)	121/153 (79.1%)	258/307 (84.0%)

N: group total

Time to remission / response (70/100) and absolute change of CDAI:

ITT analysis set		Budesonide 3 mg TID (n=78)	Budesonide 9 mg OD (n=76)	Total Budesonide (n=154)	Mesalazine 1.5 g TID (n=153)	Total (n=307)
Time to first remission [days]	Median (Q25% - Q75%)	15.0 (7 to 34)	13.0 (6.5 to 31.5)	14.0 (7 to 33)	16.0 (7 to right censored)	15.0 (7 to 43)
Time to first response (70) [days]	Median (Q25% - Q75%)	9.0 (5 to 18)	6.0 (5 to 15)	7.0 (5 to 17)	9.0 (5 to 29)	8.0 (5 to 21)
Time to first response (100) [days]	Median (Q25% - Q75%)	14.5 (6 to 32)	8.0 (6 to 25)	11.5 (6 to 30)	13.0 (7 to 53)	13.0 (7 to 34)
Absolute change of CDAI baseline to final [LOCF]	Mean (SD)	-149.87 (86.21)	-147.74 (95.43)	-148.82 (90.58)	-129.75 (107.65)	-139.32 (99.75)

Q25%: lower / 1st quartile; Q75%: upper / 3rd quartile; SD: standard deviation

Evaluator's comment

This study was well designed and conducted. The primary efficacy variable was the CDAI, which is an accepted, valid, clinically relevant parameter for the evaluation of efficacy in Crohn's disease. Mesalazine (Salofalk enteric (Eudragit) coated tablets) was also an appropriate comparator. Salofalk 500 mg enteric (Eudragit) coated tablets are registered in Australia for the treatment of acute episodes and maintenance of remission of Crohn's ileitis and colitis at daily doses between 3 and 4.5 g.

The statistical considerations although quite complex appear to have been appropriate. The primary goal of the trial was to show superiority of Budenofalk over mesalazine. However, the likelihood of the need to switch from superiority to non-inferiority (in the event that remission rates with mesalazine were higher than 40% and that the ability to demonstrate superiority of budesonide would be very low) was foreseen and planned for within the protocol. The planning took into account the considerations set out in the relevant TGA-adopted EU guidance document88. It was concluded that switch of the objective could be achieved using the same confidence interval without any need for adjustment of the Type I error providing the remission rate for Budenofalk was at least 55% and that mesalazine turned out to be more effective than expected (that is, not if Budenofalk turned out to be less effective than expected). A pre specified non-inferiority margin of –0.10 was chosen and appears to have been reasonable. Also, quite appropriately, the primary efficacy analyses were performed with the ITT as well as with the PP populations, with the requirement that non-inferiority be concluded in both analyses.

The definition of remission in this study was a CDAI ≤ 150 at the final visit (LOCF). The definition of remission set out in the relevant TGA-adopted EU guidance89 is somewhat more conservative in that it requires not only that the CDAI fall to below 150 but that is also maintained for at least 2 weeks. In this study there was no requirement for the CDAI to have been demonstrated to be less than 150 over two successive visits (which were 2 weeks apart). When the IPD CDAI data were reviewed by the clinical evaluator, it was apparent that 28 patients did not meet this stricter criterion - 8 patients in BUC 3 mg tid group; 5 in BUC 9 mg od group; and 15 in mesalazine group. This gives remission rates that are somewhat lower than reported (the rate for mesalazine becomes 80/153 (52.3%) and for Budenofalk total 94/154 (61.0%)), but the between group difference in favour of Budenofalk is maintained at 8.7%.

Another consideration is which of the response rates is most appropriate. The TGA adopted EU guideline defines a responder as a patient in whom remission has been achieved or there has been a reduction of at least 100 in the CDAI at the end of the treatment period. This equates to

[88] Points to Consider on Switching between Superiority and Non-inferiority CPMP/EWP/482/99. http://www.tga.gov.au/pdf/euguide/ewp187503final.pdf

[89] Guideline on the Development of New Medicinal Products for the Treatment of Crohn's disease (CPMP/EWP/2284/99 Rev 1). http://www.tga.gov.au/pdf/euguide/ewp228499enrev1.pdf

the responder (100) endpoint in this study. Of the 28 patients who were not remission according to the guideline definition, all but 1 in the BUC 3 mg tid group and 3 in the mesalazine group achieved a reduction in CDAI of more than 100 and therefore still contribute to the responder (100) outcome. Thus, the responder (100) rates were largely unchanged by the application of a stricter definition for remission; 59/78 (75.6%) for BUC 3 mg tid, 57/76 (75.0%) for BUC 9 mg od and 102/153 (66.7%) for mesalazine.

The clinical evaluator was satisfied that the non-inferiority of Budenofalk (given via a regimen identical to that proposed in the current application) to oral mesalazine has been demonstrated in this study. Furthermore, the benefits of Budenofalk in terms of remission, response and changes in CDAI observed in this setting can be considered to be clinically important especially given that more than 70% of the enrolled patients were less than 40 years old when first diagnosed with Crohn's disease (an age below 40 years is a predictor for a disabling course of the disease), more than 25% had a history of surgery due to Crohn's disease and around 12% of the patients suffered from actual or formerly fistulising disease.

Study BUC-23

Study design, objectives, location and dates

This Phase III randomised, double blind, double dummy, multicentre, controlled study was conducted at 14 centres in Israel from July 1995 to January 1997 with the objective of comparing Budenofalk 9 mg daily with a tapering schedule of Prednisone over 8 weeks with respect to efficacy, safety and quality of life in adult patients with active Crohn's disease.

Inclusion and exclusion criteria

Patients 18 to 70 years of age suffering from a current exacerbation of known Crohn´s disease (CDAI between 150 and 350) or with symptoms for at least 3 months in newly diagnosed patients, with localisation of disease confirmed by colonoscopy and X-ray, a negative stool culture and no current use of elemental diet, steroids or immunosuppressive agents were eligible for study entry. Patients with macroscopic Crohn's lesions of the upper gastrointestinal tract, symptomatic stenosis or other serious diseases or disturbances of hepatic and renal function were excluded. Other reasons for exclusion were: pregnancy or lactation; concomitant use of non-steroid anti-inflammatory drugs and disturbances of blood clotting.

Study treatments

Patients received either Budenofalk 3 mg tid for 8 weeks (BUC) or Prednisone 5 mg (Predniton, Vitamed Ltd, Israel) eight tablets daily in Week 1, tapering to one tablet daily at Wweek 8 (PRED). Prednisone tablets were taken as one dose once daily in the morning.

Efficacy variables and outcomes

The main efficacy variable was the CDAI. Response was defined as CDAI <150 at study end and in patients with a baseline CDAI <210, a decrease in CDAI ≥ 60. Thee types of responders were analysed:

- "R1" responder: response without the occurrence of either "moon face" or acne (considered to be the two main steroid-induced ADRs)
- "R2" responder: response associated with the occurrence of at least one steroid-induced ADR
- "R0" responder: overall response (R1 or R2 response)

The presence/development of steroid-induced ADRs was documented using a CRF that included 12 pre defined symptoms; moon face, acne, mood changes, headache, muscle weakness, dyspepsia, vertigo, swollen ankles, buffalo hump, hirsutism, skin striae and easy bruising.

Evaluator's comment

Although the CRF documented 12 pre defined ADRs, the main steroid-induced ADRs used for the R1 endpoint were moon face and acne. An analysis of the 12 pre defined symptoms found that, with the exception of moon facies and acne, these symptoms and signs were either already present at baseline or did not increase in incidence during the study. The sponsor concluded that moon face and acne showed the clearest relationship with steroid intake whilst the other symptoms were not strongly associated with study treatment. They considered it was justifiable to concentrate on moon face and acne for the main study endpoint (R1) and this seemed reasonable.

The primary efficacy outcome was the R1 responder rate at 8 weeks. Other efficacy outcomes included:

- Rates of R1 response at Weeks 2 (Visit (V) 2), 4 (V3) and 6 (V4)
- Rates of R2 and R0 response at Weeks 2, 4, 6 and 8
- Time to R0 response
- Changes in CDAI
- Change in Quality of Life at Wweek 6, assessed using one general questionnaire (SF-36) and one specifically for IBD (IBD questionnaire)

Sample size

A priori sample size calculations determined that 85 patients per treatment group were required for the study to have 80% power at the 0.05 significance level to detect a 20% difference in the R1 response rate of the two groups after 8 weeks, assuming a budesonide R1 response rate of 55-65%. Consequently, it was planned to include 100 patients per treatment group to have at least 85 evaluable cases per group.

Randomisation and blinding methods

Patients were allocated to treatment groups using a centralised, computerised block wise randomisation procedure (ratio 1:1, block size 4). Blinding was achieved though the employment of a double dummy technique whereby placebo tablets identical in size, shape and colour to prednisone were administered to the Budenofalk treatment group and placebo capsules identical in size, shape and colour to Budenofalk capsules were administered to the prednisone treatment group.

Statistical methods

R1, R2 and R0 response rates were compared using (Fisher´s exact test). Secondary efficacy and safety variables were presented using descriptive summary statistics. Analyses were conducted on ITT and PP populations.

Participant flow

A total of 201 patients were enrolled in the trial, with 100 randomised to treatment with BUC and 101 to treatment with PRED. The number of patients enrolled per centre ranged from 7 to 31 and only 2 centres enrolled 20 or more patients. All 201 patients formed the ITT population. During the study, 23 patients from each treatment group discontinued treatment prematurely. The primary reasons for discontinuation were lack of efficacy (15 in each group), adverse event (4 in each group) and non-compliance (4 in each group).

Protocol deviations were documented in 87 patients (47 BUC versus 40 PRED), with major protocol deviations occurring in 30 patients (16 BUC versus 14 PRED). The major deviations included intake of non permitted medication (5 BUC; 4 PRED), baseline CDAI <150 or >350 (3 PRED and location of the disease to the upper small intestine (3 BUC). Patients with major

protocol deviations were excluded from the PP population, leaving 171 patients (84 BUC and 87 PRED).

Baseline data

The two treatment groups were well matched at baseline with respect to demographic and key disease characteristics. There was an even balance of gender and the mean age was 33 years in both groups. The average time between the first diagnosis and study entry was 5 years in both treatment groups (median 2 and 3 years respectively) and the almost half the patients in each group had had symptoms from their current exacerbation for less than 3 months and 25% for more than 6 months. Approximately 54.0% of BUC patients and 51.5% of PRED patients had inflammation of the lower small intestine, caecum and/or ascending colon only. A further 34.0% of BUC patients and 31.7% of PRED patients also had disease of more distal parts of the colon. Mean (± SD) CDAI at baseline was 264 (± 52.8) for the BUC group and 265 (± 58.0) for the PRED group. Extra intestinal disease manifestations and previous treatments were also similar.

Results for the primary efficacy outcome. R1 response rates

Response rates and changes in CDAI are shown in Table 41. The R1 response rate (response without steroid-induced ADRs) at 8 weeks was twice as high in the BUC group (30.0%) compared to the PRED group (13.9%), p = 0.004 (ITT analysis). Similar results were observed for the PP analysis set (33.3% versus 13.8%, p=0.002) as well as in most subgroup analyses of the effect of Crohn's disease duration, severity, localisation and presence of extra intestinal manifestations (Tables 42 and 43). One study site had no documented responders in either group. Of the remaining 13 sites, 3 had R1 response rates favouring PRED and 10 had response rates favouring BUC. A formal analysis for treatment centre interaction was not performed because of small numbers in some centres.

Table 41. Efficacy results for confirmatory Study BUC-23

	BUC (n = 100)	PRED (n = 101)	p
Response at Week 8			
R1 – response without moon face or acne	**30 (30.0%)**	**14 (13.9%)**	**0.004**
R2 – response with at least one steroid induced ADR	21 (21.0%)	39 (38.6%)	
R0 – overall response	51 (51.0%)	53 (52.5%)	
Response at Week 6			
R1	29 (29.0%)	14 (13.9%)	
R2	16 (16.0%)	41 (40.6%)	
R0	45 (45.0%)	55 (54.5%)	
Response at Week 4			
R1	31 (31.0%)	26 (25.7%)	
R2	12 (12.0%)	27 (26.7%)	
R0	43 (43.0%)	53 (52.5%)	

	BUC (n = 100)	PRED (n = 101)	p
Response at Week 2			
R1	37 (37.0%)	33 (32.7%)	
R2	1 (1.0%)	16 (15.8%)	
R0	38 (38.0%)	49 (48.5%)	
Change in CDAI (baseline to last observation)			
n	95	97	
Mean ± SD	-96.1 ± 107.7	-110.9 ± 92.1	
Median	-105	-111	
Range	-321 - 198	-312 - 160	

Table 42. Efficacy outcomes by location of disease in confirmatory Study BUC-23

Location of the disease		Budesonide, n=100		Prednisone, n=101	
		n	%	n	%
lower intestine/ cecum/ascending colon	R0-responder	30	55.6	26	50.0
	R1-responder	19	35.2	8	15.4
	R2-responder	11	20.4	18	34.6
lower intestine, ascending/trans-verse/descending colon, cecum, sig-moid and rectum	R0-responder	16	47.1	20	62.5
	R1-responder	7	20.6	3	9.4
	R2-responder	9	26.5	17	53.1
mouth, upper/ middle/lower intes tine, cecum and ascending colon	R0-responder	4	66.7	4	40.0
	R1-responder	3	50.0	3	30.0
	R2-responder	1	16.7	1	10.0
mouth, upper/ middle intestine	R0-responder	1	100.0	-	-
	R1-responder	1	100.0	-	-
	R2-responder	-	-	-	-
transverse/des-cending colon, sig moid and rectum	R0-responder	-	-	3	60.0
	R1-responder	-	-	-	-
	R2-responder	-	-	3	60.0

Table 43. Outcomes in BUC-23 by disease activity, durat'n and manifestations at baseline

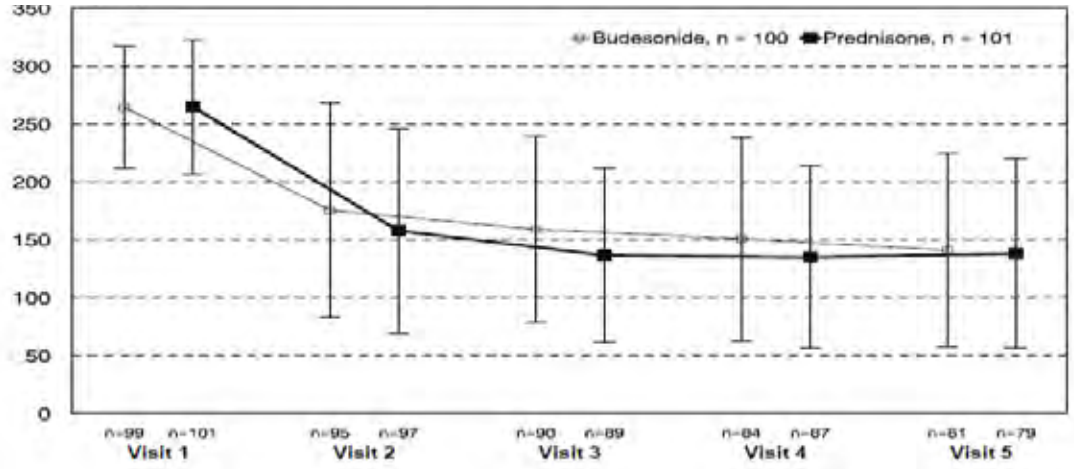
Remaining secondary parameters		Budesonide, n=100		Prednisone, n=101	
		n	%	n	%
CDAI < 300 at baseline	R0-responder	38	54.3	39	57.4
	R1-responder	24	34.3	12	17.6
	R2-responder	14	20.0	27	39.7
CDAI ≥ 300 at baseline	R0-responder	13	44.8	14	42.4
	R1-responder	6	20.7	2	6.1
	R2-responder	7	24.1	12	36.4
patients with ex-traintestinal mani-festations at base.	R0-responder	12	54.5	8	36.4
	R1-responder	6	27.3	4	18.2
	R2-responder	6	27.3	4	18.2
patients without extraintest. mani-fest. at baseline	R0-responder	39	50.0	45	57.0
	R1-responder	24	30.8	10	12.7
	R2-responder	15	19.2	35	44.3
duration of the disease < 8 years	R0-responder	42	52.5	46	59.7
	R1-responder	25	31.3	10	13.0
	R2-responder	17	21.3	36	46.8
duration of the disease ≥ 8 years	R0-responder	9	45.0	7	30.4
	R1-responder	5	25.0	4	17.4
	R2-responder	4	20.0	3	13.0

Results for other efficacy outcomes. ITT population

Table 41 also shows there were more R1 responders in the BUC group and more R2 responders in the PRED group at the end of the study (Week 8) and at individual study visits at Weeks 2, 4 and 6. Overall response (R0) was comparable between the two groups but a greater proportion of these patients in the PRED group experienced steroid induced ADRs than in the BUC group.

There was a higher change in CDAI from baseline to the last observation in the PRED treatment group (-110.9 ± 92.1 score points) than in the BUC treatment group (-96.1 ± 107.7 score points) and the mean time to achieving a CDAI-value < 150 (the time to response) was 24 ± 13.2 in the BUC group versus 21 ± 11.7 days in the PRED group with clearly more patients reaching response in the Prednisone group before the 2 week visit (28 versus 40). Most of the improvement in CDAI was seen in the first two weeks, with a gradual further decrease in the following 6 weeks of treatment (Figure 19). Changes in the 8 clinical parameters used for calculating the CDAI showed a similar pattern.

Figure 19. Change in CDAI (ITT analysis, n=201) in confirmatory Study BUC-23



In the subgroup analyses of R0 remission rates, the efficacy of Budenofalk was similar to that of prednisone when the disease was localised only in the terminal ileum and/or caecum and/or ascending colon (55.6% versus 50.0%) but Budenofalk appeared to be less effective than prednisone when the disease involved the distal colon and rectum as well (47.1% versus 62.5%). Both medicines were less effective in patients with more active disease (CDAI >300).

The SF-36 and IBDQ showed very similar values for the two treatments at the final visit but a more pronounced difference between baseline and last visit sum scores were seen in favour of prednisone. However, baseline values were also lower in this group.

Evaluator's comment

Overall, this study was well designed and conducted and employed a dosage regimen for Budenofalk that is identical to that proposed in the current application for registration.

Prednisone and Budenofalk achieved similar overall response rates (R0). Prednisone achieved a response slightly quicker than Budenofalk but more patients experienced typical steroid ADRs. The advantage of this trial is that the primary outcome (R1) was a benefit-risk outcome, that is, the induction of remission of disease without the steroid-induced ADRs of moon face and acne. In this regard Budenofalk was superior to prednisone.

The main issue with this study is that the prednisone brand used (Predniton) is not marketed in Australia. However, prednisone is well absorbed from immediate release preparations with systemic bioavailability of 84 ± 13% (Czock et al 2005[90]) and thus the outcomes for Predniton can reasonably be extrapolated to the products available in Australia.

Exploratory efficacy studies

Study BUC-16/CDA

This double blind, multi centre, randomised, placebo controlled study, consisting of a 56 day treatment phase and a 14 day follow-up dose reduction phase was conducted in 12 centres in Russia, 4 in the Ukraine and 1 in Belarussia from August 1995 to August 1997. The objective of the study was to compare the safety and efficacy of Budenofalk at 3, 9 and 18 mg daily versus placebo in adults with active Crohn's disease and thereby help determine the optimum daily dose of Budenofalk for inducing remission in such patients. Inclusion and exclusion criteria were generally consistent with those used in the pivotal studies.

Patients were randomised to receive daily doses of either 3 mg budesonide (1 x 1 mg Budenofalk tid; n= 104), 9 mg budesonide (1 x 3 mg Budenofalk tid; n=104), 18 mg budesonide (2 x 3 mg Budenofalk tid; n=99) or placebo (n=102) for 56 days, followed by a dose reduction period, during which patients in the 9 mg and 18 mg budesonide treatment groups received a daily dose of 6 mg budesonide (2 x 1 mg Budenofalk tid) and patients in the 3 mg budesonide and placebo groups received placebo for 14 days. A combination of Budenofalk and identical placebo capsules was used so that all patients took two capsules orally thee times a day.

Assessments of CDAI, stool count and consistency, abdominal pain, CRP and ESR were performed at screening/baseline (Day -7), randomisation (Day 0) and at Day 14 (± 3), Day 28 (± 7), Day 42 (± 7), Day 56 (± 7) and Day 70 (± 7) and the primary efficacy outcome was the proportion of patients in clinical remission (defined as a CDAI score of ≤150 and a decrease of at least 60 points from baseline) at the end of the treatment period (Day 56). Other efficacy outcomes included (but were not limited to) mean change from baseline in CDAI score at each study visit, time to first clinical remission and the proportion of patients with therapeutic

[90] Czock D, Keller F, Rasche FM and Haussler U. Pharmacokinetics and Pharmacodynamics of Systemically Administered Glucocorticoids. *Clin Pharmacokinet* 2005; **44(1)**: 61-98.

benefit (defined as a decrease in the CDAI of ≥60, irrespective whether or not remission was achieved) at each study visit.

A priori sample size calculations indicated 98 evaluable patients would be required in each treatment group to give 80% power at a significance level of 0.05 to demonstrate a difference in response rates between the optimal dose and placebo of at least 25%, assuming that at least 50% of patients would respond to the optimal dose of budesonide and less than 25% would respond to placebo.

The ITT population comprised 102 patients in the placebo group, 104 in the 3 mg budesonide group, 104 in the 9 mg budesonide group and 99 in the 18 mg budesonide group. Fifty-two patients were withdrawn prematurely during treatment due to lack of co-operation (21), lack of efficacy (16), intolerable adverse events (12) and other reasons (3). Major protocol deviations were observed in 61 patients, most commonly due to patient failure to complete their dairy and use of non permitted medication, with all treatment groups being more or less equally affected.

The treatment groups were well balanced with regard to demographic and disease characteristics at baseline and overall, the study population was characterised by a relatively low entry CDAI and a low CRP value, indicating only a very mild inflammation.

No dose response relationship was found for remission rates at 8 weeks (ITT analysis); 35% for placebo, 51% for Budenofalk 3 mg daily, 37% for Budenofalk 9 mg daily and 44% for Budenofalk 18 mg. Furthermore, only the statistically significant difference in remission rates was found between the placebo group and the Budenofalk 3 mg group ($p = 0.022$) and no statistically significant differences were found between any of the Budenofalk groups and the placebo group in the PP analysis. Overall, 165 of 361 (46%) of the patients with a CDAI <300 at baseline responded to treatment. However, the number of patients with a CDAI >300 (48 patients in all 4 treatment groups) was too small to perform a reasonable statistical evaluation for differences between the treatment groups. Duration of disease (>9 years or <9 years) and presence or absence of extra intestinal manifestations at baseline had no clear influence on clinical remission rates.

In keeping with the primary endpoint analysis, no dose response relationships were observed for any of the secondary endpoints. Although the proportions of patients experiencing therapeutic benefit in each of the Budenofalk groups was higher than observed with placebo, a statistically significant difference compared to placebo was achieved only with Budenofalk 3 mg daily. The time to first therapeutic benefit was the shortest for Budenofalk 3 mg (28 days versus 30 days for Budenofalk 9 mg, 32 days for Budenofalk 18 mg and 33 days for placebo). By Day 70, following dose tapering the proportion of patients in clinical remission had increased in all groups compared to Day 56, including the placebo group for which the response rate had risen from 35% to 43%.

Evaluator's comment

In this study only budesonide 3 mg was shown to be statistically significantly better than placebo in the treatment of active Crohn's disease in terms of remission rates and therapeutic benefit and there was no evidence of a dose response relationship for the primary and secondary efficacy outcomes. This result was unexpected as it conflicted with evidence from other trials.

These efficacy findings need to be interpreted in the context that there was clear evidence of a dose dependent increase in typical steroid-related AEs such as depression of the adrenal function and osteocalcin levels (see PD section of this CER). Thus, it is unlikely there was a problem with study drug quality or that there had been any inadvertent mix up of the study medication due to a packaging or labelling error. This was confirmed by the sponsor's re-analysis of returned medication of those patients whose responses were contrary to expectation.

The sponsor also undertook other additional analyses that involved review of the CRF documentation and patients' charts. It was concluded that patients were correctly diagnosed with Crohn's disease but in the majority of patients only mild inflammation was present. Generally, the nutritional status of patients was poorer and patients were more anaemic and more underweight than found in studies conducted in Western Europe and it was postulated this may have contributed to the findings. (Note: the dose finding study for Budenofalk rectal foam (BUF-5/UCA) also conducted in the former Soviet Union failed to demonstrate a dose response relationship as well and this was attributed to a high placebo response rate due to a high hospitalisation rate and resultant intensive medical care; see CER (Foam)). Non-compliance with banned concomitant medications was considered unlikely but could not be ruled out entirely. It was also noted that the subjective assessment of general well being and abdominal pain contributed to the high frequency of responders in the placebo and Budenofalk 3 mg groups.

As previously noted, a 1 mg Budenofalk capsule was used to achieve the 3 mg daily dose and the tapered dose (2 mg) for the final 14 days in patients treated initially with daily doses of 9 mg and 18 mg Budenofalk. No pharmacokinetic or pharmaceutical chemistry data were presented to support the use of the 1 mg strength in this study.

Study BUC-15/CDA

This triple arm, randomised, double-blind, stratified, multicentre study was conducted in 62 sites in Germany and 1 centre in Austria from October 1994 to November 1995 with the primary aim of investigating which daily dose of Budenofalk (6 mg, 9 mg or 18 mg) was most suitable for inducing clinical remission in adults with active Crohn's disease and for switching steroid dependent patients with active or post active Crohn's disease to a locally acting steroid of similar or better efficacy than systemically acting steroids, whilst simultaneously reducing steroid induced side effects.

The entry criteria employed in this study were similar to those used in the pivotal and other exploratory studies, except that patients were required to have either with an acute exacerbation (CDAI ≥ 150) or steroid dependent disease (previous treatment for at least 2 weeks with not more than 30 mg daily or not less than 5 mg daily of prednisolone or prednisolone equivalent).

Patients were randomised to receive either 6 mg budesonide (2 x 1 mg Budenofalk tid; n= 109), 9 mg budesonide (1 x 3 mg Budenofalk tid; n=100) or 18 mg budesonide (2 x 3 mg Budenofalk tid; n=109) for 12 to 15 weeks. A combination of Budenofalk and identical placebo capsules was used so that all patients took two capsules orally thee times a day. Within each treatment group patients were stratified according to whether they had received no steroid treatment within the last 2 weeks (Stratum 1) or had received steroid treatment within the last 2 weeks (Stratum 2). Patients in Stratum 1 were treated with Budenofalk for 12 weeks. For patients in Stratum 2 , the first part of the trial was used to switch from systemically acting glucocorticosteroid to Budenofalk according to a specified reduction scheme. Depending on the previous corticosteroid dose, this overlapping treatment phase lasted not more than 3 weeks. This was followed by a single treatment phase with Budenofalk lasting for 12 weeks.

The primary efficacy outcome was the response rate after 6 weeks of Budenofalk monotherapy where response was defined as a CDAI < 150. Other efficacy outcomes included (but were not limited to) treatment failure rates where treatment failure was defined as withdrawal of treatment before week 6 or CDAI ≥ 150 or missing CDAI data at Week 6, response rates after 12 weeks of Budenofalk monotherapy and time to response.

A priori sample size calculations indicated that 86 patients per treatment group were required for the study to have 80% power (at the 0.05 level of significance) to detect a 20% lower response rate in the 6 mg treatment group compared to the 9 mg group, assuming the response rate in the 9 mg group was 65%.

Of the patients randomised to treatment, 4 (1 from the 6 mg group and 3 from the 18 mg group) did not take any medication, leaving 314 "evaluable" patients. One "evaluable" patient from the 9 mg Budenofalk group was lost to follow-up and was excluded from the safety analysis because no data for any safety outcomes were available. This left 313 patients in the safety population (6 mg Budenofalk n=108; 9 mg Budenofalk n=99; and 18 mg Budenofalk n=106).

Evaluator's comment

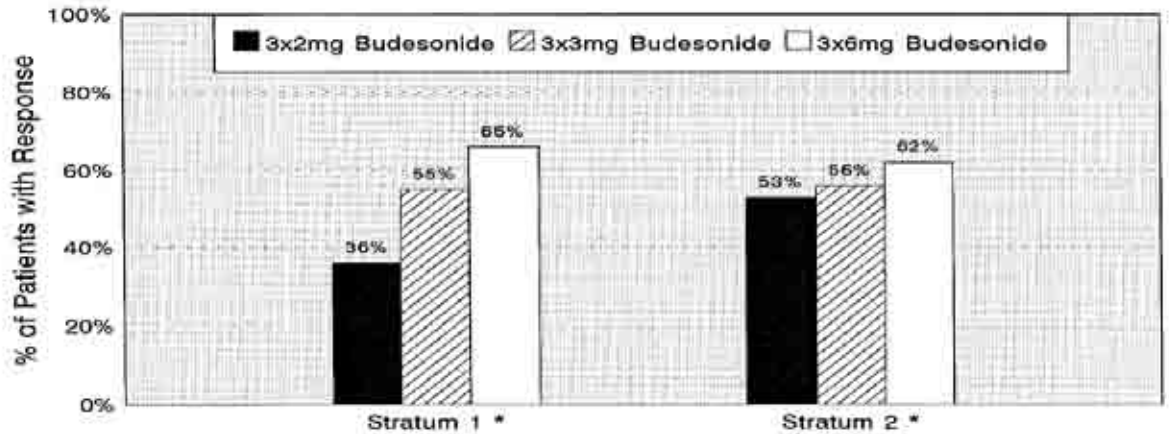
The indication sought for Budenofalk in this application is for the induction of remission in patients with active disease and not for its use in post active steroid dependent patients. Thus, the data most relevant to this application are those pertaining to stratSm 1 and these data are highlighted below. Note that the sample size calculations were performed for the overall study population and thus the absence of statistical significance for some efficacy outcomes for stratSm 1 needs to be interpreted in that context.

The ITT population for Stratum 1 comprised 104 Caucasian patients, 37 (35.6%) of whom were male and 67 (64.4%) female. Mean (± SD) age was 33 ± 9.4 years in the 6 mg group, 3l ± 7 .4 years in the 9 mg group, and 34 ± 7 .9 years in the 18 mg group. The median (range) time since confirmation of diagnosis of Crohn's disease was 76 (1 – 327) months in the 6 mg group, 75 (7 – 213) months for the 9 mg group, and 73 (9 – 260) months for the l8 mg group. The mean (± SD) CDAI at baseline was 257 ± 77.3 in the 6 mg group, 268 ± 74.7 in the 9 mg group, and 239 ± 2.7 in the 18 mg group, whilst mean (± SD) baseline CRPs were 27 ± 27.4 mg/L in the 6 mg group, 35 ± 59.7 mg/L in the 6 mg group, and 30 ± 23.9 mg/L in the 18 mg group.

Results for the primary and some secondary efficacy outcomes in Strata 1 and 2 are summarised and contrasted in Figure 20. After 6 weeks of treatment with budesonide monotherapy, there was a clear dose response relationship for clinical remission rates in patients in Stratum 1 (ITT population): 14/39 (36%) in the 6 mg group, 18/33 (55%) in the 9 mg group and 21/32 (66%) in the 18 mg group. However, a statistically significant treatment difference was detected only for the comparison of the 18 mg group with the 6 mg group (p=0.017). Similar results were obtained for the overall study population; 46.7% responders in the 6 mg group, 55.6% in the 9 mg group and 63.2% in the 18 mg group (p = ns for 6 mg versus 9 mg; p = ns for 18 mg versus 9 mg; p=0.019 for 18 mg versus 6mg). Other findings were:

- reductions in the mean and median CDAIs of the 9 mg and 18 mg groups were similar in magnitude and greater than in the 6 mg group. After 6 weeks, the mean CDAI was significantly lower in the 9 mg and 18 mg groups than in the 6 mg group (p=0.0058 and p=0.0008, respectively);
- median times to remission were notably shorter for the 9 mg and 18 mg dose regimens (22 and 2l days respectively) than for the 6 mg dose regimen (39 days);
- mean CRP level decreased to a similar degree in the 9 mg and 18 mg groups during the first 6 weeks of therapy, whereas mean CRP level increased the 6 mg group; and
- a dose response relationship was observed with respect to changes in median CRP levels and mean and median ESR values.

Figure 20. % responders at Week 6 by stratum in dose-finding study BUC-15/CDA



Subgroup analyses of remission rates indicated the efficacy of the 3 budesonide doses did not differ significantly in patients with an entry CDAI <300 or in patients with Crohn's disease affecting the ileum and right colon. Patients with high disease activity (CDAI ≥ 300) at study entry and patients with disease affecting the transverse colon to the rectum responded better to the 18 mg dose of budesonide than to the 6 mg dose during the first 6 weeks of therapy.

Evaluator's comment

As previously noted a 1 mg Budenofalk capsule was used to achieve the 6 mg daily dose. No pharmacokinetic or pharmaceutical chemistry data were presented to support the use of the 1 mg strength in this study.

Notwithstanding this issue, the study demonstrated the dose dependency of the efficacy of Budenofalk capsules in active Crohn's disease, with higher response rates and greater improvements in CDAI and laboratory markers of disease activity (ESR and CRP) at 6 weeks in patients receiving 9 mg and 18 mg Budenofalk daily compared to those receiving 6 mg daily. Furthermore, the similarity of outcomes (in terms of remission rates and changes in CDAI, CRP and ESR) for the 9 mg and 18 mg groups, coupled with the higher rate of typical steroid induced systemic side effects in the 18 mg group (see below) suggested a 9 mg daily dose would give the optimal benefit-risk balance.

However, also of note, the overall responder rates (Stratum 1 and 2 combined) actually decreased in all 3 groups with continued treatment beyond week 6 to week 12. The response rates dropped from 46.7% to 35.2% in the 6 mg group; 55.6% to 49.5% in the 9 mg group and 63.2% to 47.2% in the 18 mg group, with only the difference between the 6 mg and 9 mg group reaching statistical significance (p=0.027). There was no breakdown of the 12 week response rate by stratum in the study report itself. However, using textual information and tabulations elsewhere in the study report, the clinical evaluator determined that of a total of 35 additional treatment failures at Week 12, 15 were in Stratum 1 and 20 were in in Stratum 2. The response rates at Week 12 in Stratum 1 were 23.1% in the 6 mg group (down from 36% at week 6), 48.4% in the 9 mg group (down from 55% at Week 6) and 40.6% in the 18 mg group (down from 66% at Week 6). The reasons for the additional treatment failures in Stratum 1 were increases in CDAI to above 150 (n=12) and premature discontinuation (n=3). Of the 10 increases in CDAI, all but 2 remained below 200.

Gross V, Andus T, Caesar I, et al. Oral pH-modified release budesonide versus 6-methyl prednisolone in active Crohn's disease. European Journal of Gastroenterology & Hepatology 1996; 8: 905-909

This randomised, double blind, double dummy, multicentre study was conducted in Germany and Austria to compare the efficacy and safety of oral Budenofalk capsules and 6-methyl-

prednisolone in adult patients with active Crohn's disease. The manuscript for this paper was received in January 1996 and accepted for publication in June 1996.

The entry criteria employed in this study were similar to those employed in the pivotal and other exploratory studies. Patients were randomised to receive either Budenofalk 3 mg tid, taken 30 minutes before meals for 8 weeks or a weekly tapering schedule of 6-methylprednisolone over 8 weeks (48-32-24-20-16-12-8-8mg), administered as a single dose in the morning 30 min before breakfast.

The main efficacy variable was the CDAI and the primary efficacy outcome was the response rate after eight weeks of therapy, where response was defined by a CDAI below 150 points and a minimum CDAI decrease by 60 points in patients with an entry CDAI of 210 points. Other efficacy outcomes (assessed at 2, 4, 6 and 8 weeks) included the mean CDAI, time to response and time to failure and effects on inflammatory parameters (CRP, leukocyte count. Treatment failure was defined as a CDAI > 150 points after eight weeks or a CDAI decrease of less than 60 points in patients with an entry CDAI < 210 points, a fever > 39°C lasting six days, a CDAI increase above 350 points (with increase of ≥ 20% of the previous CDAI), CDAI increase by > 100 points during two weeks, occurrence of complications, need for surgery, withdrawal because of severe extra-intestinal manifestations requiring a different therapy or discontinuation due to severe side effects.

A total of 67 patients (with CDAI > 150 who received at least one daily dose of study medication) were used for the ITT analysis. Limited information was provided otherwise; 9 patients in the Budenofalk group and 2 in the 6-methylprednisolone group withdrew early from the study. Reasons for early withdrawal included the need for surgery (one patient from each group), non compliance (one patient from each group), ileus (n=1), side effects (n=1) and CDAI increase by >100 (n=5); all from the budesonide group.

Both treatment groups were comparable at baseline with respect to age (mean ± SD: BUD 31 ± 9.5 yrs versus 6-MP 3l ± 10.6 yrs), duration of Crohn's disease (BUD 94 ± 70 mo versus 6-MP 78 ± 62 mo), CDAI (BUD 263 ± 49 versus 6-MP 262 ± 81) and prevalence of extra intestinal manifestations (BUD 52.9% versus 6-MP 42.2%). In excess of 50% patients in each group had involvement of the sigmoid colon and approximately 40% had involvement of the rectum.

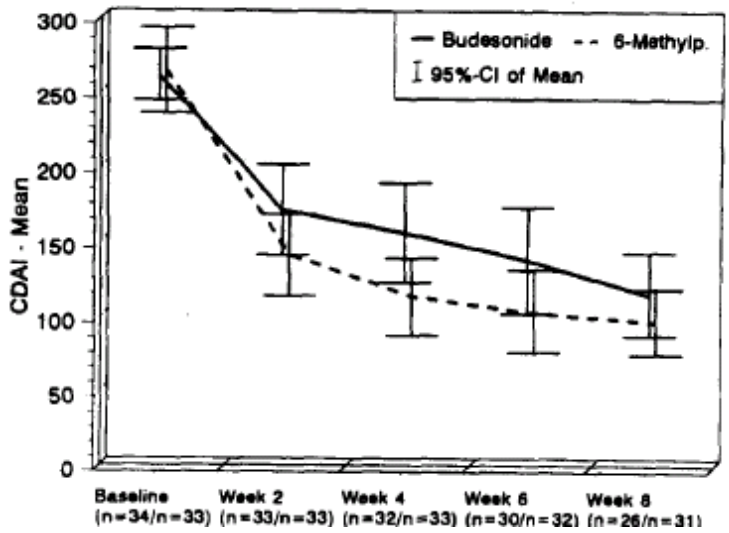
After 8 weeks of study treatment, the response rates were 19/34 (55.9%; 95%CI 37.9 – 72.8%) for the Budenofalk group and 24/33 (72.7%; 95%CI 54.5 – 87.7%) for the 6-methylprednisolone group (p = 0.2366). Conversely, therapeutic failures were observed in 44.1% Budenofalk patients and 27.3% of 6-methylprednisolone patients, with the most common reason for failure being that the last documented CDAI was >150 (Table 44). Disease localisation, the presence of extra intestinal manifestations and entry CDAI had no effect on response rates.

Table 44. Treatment failures Gross et al 1996

	Budesonide (*n*=15)	6-Methyl-prednisolone (*n*=9)
Last documented CDAI≥ 150	14 (93.3%)	7 (77.8%)
CDAI decrease of <60 points	0	2 (22.2%)
No follow-up CDAI available	1 (6.7%)	0
Early withdrawal		
because of:	9	2
Need for Surgery	1	1
Ileus	1	0
CDAI increase by >100 points	5	0
Side effects (weight gain, hypotension, psychologic, disturbance)	1	0
Non-compliance	1	1

The (mean ± SD) CDAI decreased from 263 ± 50 at study entry to 118 ±69 after 8 weeks in the Budenofalk group and from 262 ± 81 at study entry to 95 ± 61 after 8 weeks in the 6-methylprednisolone group (p = 0.183). The time course for reduction in CDAI is presented in Figure 21 which shows numerically greater reductions in the 6-methyl-prednisolone group at each visit over the 8 weeks of treatment, however these differences were not statistically significant. The time course of CDAI and the time to response (BUD 22.3 ± 12.1 days versus 6MP 20.0 ± 10.7 days) showed that the majority of the beneficial effects of both treatments were observed in the first 2 weeks of treatment. Greater decreases in CRP levels were observed in the 6-methylprednisolone group (mean reduction 4.64 mg/100mL) than in the Budenofalk group (0.31 mg/100mL). Mean leucocyte counts increased by 61.9% after 2 weeks treatment with 6-methylprednisolone and only 11.7% after 2 weeks treatment with Budenofalk.

Figure 21. Changes in mean CDAI Gross et al 1996



Evaluator's comment

This published article was based on the sponsor's Study BUC-2. This study was nominated by the sponsor as a pivotal study but the sponsor chose to submit a published paper in preference

to the full study report. The paper demonstrates some of the shortcomings of published literature:

- randomisation details (whether computerised, centralised etc) were not provided so it was not possible to assess the potential for corruption of the process (however, some reassurance is provided by the comparability of treatment groups);
- there was no information about the choice of sample size (such as *a priori* calculation);
- there was minimal information about participant flow, with no mention of the number of patients screened (or reasons for ineligibility) and no analysis of protocol deviations and violations. The paper merely stated the ITT population size; and
- there was no information about how compliance was monitored, that is, by diary, return and checking of unused medication etc.

The absence of such information prevents a complete evaluation of the study results.

The published paper indicated the study had only 73% power to detect a 30% difference at the 0.05 significance level. It is clear the study was underpowered to detect a smaller and clinically relevant difference between the two treatment regimens. It is not surprising, therefore, that the observed between group difference of 16.8% in response rates was not statistically significant. The small sample sizes are reflected in the width of 95%CI for the Budenofalk response rate (37.9-72.8%) and for the between group difference, calculated by the clinical evaluator as 16.8 ± 22.5%. The latter suggests the true population difference could lie anywhere between 39.3% in favour of 6-methyl-prednisolone and 5.7% in favour of Budenofalk. Thus, the conclusion stated in the sponsor's Summary of Clinical Efficacy that "Oral pH-modified release budesonide (3 mg TID) is almost as effective as the conventional corticosteroid 6-methylprednisolone in patients with mild to moderately active ileocolonic Crohn's disease" is fairly meaningless (the italicising is the clinical evaluator's emphasis). At best, this was a hypothesis-generating, exploratory study.

Caesar I, Roth M, Andus T, et al. Treatment of Active and Postactive Ileal and Colonic Crohn's Disease with Oral pH-modified-release Budesonide. Hepato-Gastroenterology 1997; 44: 445-451

This open, uncontrolled, multicentre trial was conducted in Germany with the primary aim of assessing the efficacy of Budenofalk in inducing clinical remission after 6 weeks in adults with active Crohn's disease. Secondary aims were to assess the maintenance of clinical remission after tapering the drug to a lower dosage in a second 6 week study phase and to evaluate the influence of disease characteristics on remission rate.

The entry criteria employed in this study were similar to those employed in the pivotal and other exploratory studies except that patients were required to have a CDAI >200 without glucocorticoid treatment in the previous 2 weeks. Patients received Budenofalk oral capsules at a dose of 3 mg (1 x 3 mg capsule) tid for 6 weeks and those in clinical remission after 6 weeks continued treatment at a dose of 2 mg tid for a further 6 weeks.

The primary efficacy outcome was the proportion of patients in clinical remission (CDAI <150) at 6 weeks. Other efficacy outcomes included time to remission; mean and median CDAI scores at 2, 4 and 6 weeks; clinical parameters (such as stool counts etc) at 2, 4, 6 and 12 weeks; and the proportion of patients with failure of therapy at 6 or 12 weeks. Treatment failure was defined as a CDAI > 150 points; CDAI increase by ≥ 100 points over the entry CDAI during the trial; fever > 39^{o}C lasting 7 or more days; development of new fistulas or abscesses; or the need for surgery.

A total of 93 patients were recruited. The study population had a predominance of females (approximately 2:1) and mostly younger adults (average age was early 30s) with moderately active Crohn's disease (average CDAI = 260) and an average duration of disease of 9 years

(Table 45). Some 33% of patients had involvement of the small bowel, caecum, and/or ascending colon, while 63% had involvement of the transverse colon and rectum. Extra-intestinal manifestations were present at study entry in 42% of patients.

Table 45. Demographic and disease characteristics at baseline Caesar et al 1997

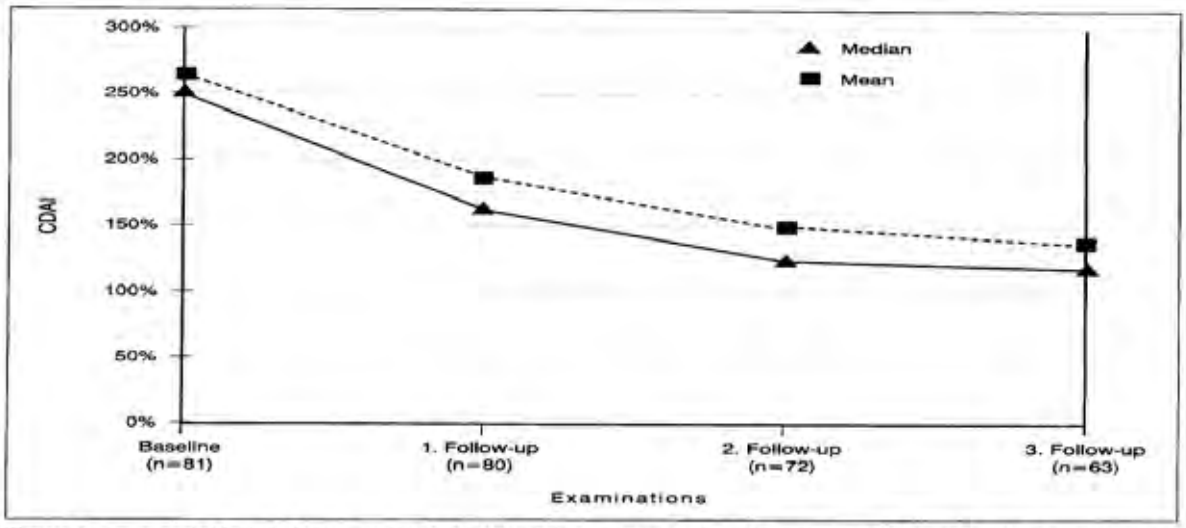
	intention-to-treat (n = 81)	per-protocol (n = 40)
sex (f/m)	55/26	28/12
age (years)*	32.7 ± 8.9	32.8 ± 8.6
duration since diagnosis (years)*	5.9 ± 5.7	6.5 ± 6.4
duration of symptoms (years)*	8.7 ± 6.5	9.5 ± 7.3
duration of acute attack (weeks)*	11.0 ± 10.7	10.1 ± 10.3
extent of disease**		
• upper GI tract	10 %	5 %
• only small bowel, coecum		
• and/ or colon ascendens	33 %	38 %
• colon transversum - rectum	63 %	63 %
extraintestinal manifestations	42 %	45 %
CDAI*	260 ± 59	270 ± 46

* mean ± SD ** multiple nominations possible

A total of 12 patients were excluded from analyses for various reasons, including CDAI ≤ 150 at study entry, incomplete documentation and insufficient medication. Thus, for the first 6 week (3 mg tid) phase, 81 patients were included in ITT analysis of efficacy, 40 in the PP analysis (patients that met all the selection criteria and were treated according to the protocol) and 89 in the safety analysis.

After 6 weeks of treatment with Budenofalk 3 mg tid, 44/81 (54.3%) patients were in clinical remission (ITT analysis). The mean and median CDAI fell progressively over the course of the first 6 weeks from 260 ±59 at study entry to 135 ± 96, with the greatest fall during the first two weeks (Figure 22). Similar changes in the main CDAI parameters (general well being, stool count and abdominal pain) were observed. Mean time to clinical remission in the acute phase was 22 days, with more than 60% patients in clinical remission after 4 weeks. The duration, severity and anatomic location of disease and the presence of extra intestinal manifestations at study entry did not significantly influence the remission rate. Reasons for treatment failure include failure to achieve CDAI<150 (62%) and increase in CDAI >100 (16%).

Figure 22. Changes in CDAI (ITT) Caesar et al 1997



In the second phase (2 mg tid for 6 weeks) 35 patients who completed the first 6 week phase of the study with a CDAI <150 were included in ITT group. During this phase 26/35 (71.4%) patients remained in remission until the end of the trial. However, of note, the mean scores in the CDAI parameters showed a numerical increase (worsening of scores) by the end of the second 6 week period. Mean CDAI scores at 12 weeks were not presented in the paper but it was noted that the CDAI increased again.

Evaluator's comment

This study is at best a supporting/exploratory study because of its open label and uncontrolled design. Such studies are known to be subject to observer and measurement bias and regression to the mean. Open studies are known to overstate the treatment effect and they are therefore a lower level of evidence than data from randomised double-blind controlled studies.

Deficiencies of the published paper include:

- absence of information about the choice of sample size (such as whether by *a priori* calculation or otherwise);
- minimal information about participant flow, with no mention of the number of patients screened (or reasons for ineligibility) and no analysis of protocol deviations and violations; and
- no information about how compliance was monitored, that is, by diary, return and checking of unused medication etc.

The dosage regimen used in this study was different to that proposed in this application.

Other efficacy studies

The sponsor submitted a number of published studies reporting outcomes from the use of Entocort oral capsules in active adult Crohn's disease. Further to earlier comments about whether studies for Entocort should be used to support this application, the TGA has already undertaken an extensive evaluation of Entocort and found its efficacy and safety in relation to its use in the induction of remission in adult Crohn's disease to be acceptable. Of the 8 supporting studies included with the present application, 5 were submitted in the form of spnsor study reports for the registration of Entocort:

- Greenberg et al 1994 (08-CR-3001);
- Rutgeerts et al 1994 (08-CR-3002);
- Campieri et al 1997 (08-CR3013);
- Lofberg, Danielsson and Salde 1993 (850-CR-7019); and
- Van Ierssel et al 1995 (08-CR-3002 (subset) - although it cannot be conclusively confirmed, it appears this publication reported on suppression of peripheral blood natural killer cells).

There is little to be gained from re-evaluating either these data or additional efficacy data for Entocort published after the TGA's registration of that product, thus the submitted studies will not be evaluated in this CER.

Analyses performed across trials (pooled analyses and meta-analyses)

Four published meta-analyses (Papi et al 2000[50]; Otley and Steinhart 2006[51]; Otley and Steinhart 2008[52]; and Seow et al 2008[53]) and a systematic literature review (Kane et al 2002) were submitted. Of note, most of these analyses were based on studies of Entocort, with relatively less contribution from studies of Budenofalk. Also, collectively, these analyses have been performed over an extended period of time and thus successively update earlier analyses. This is particularly the case with the papers by Otley and Steinhart 2006[51]; Otley and Steinhart

2008[52]; and Seow et al 2008[53] which are all based on the work of the Cochane Collaboration. Thus, only the most recent Cochane Review by Seow et al 2008[53] is summarised here.

The key conclusions by Seow et al 2008 were:

- budesonide is more effective than placebo for induction of remission in active ileo-caecal Crohn's disease. This was based on 2 studies of Entocort (Greenberg et al 1994[42] and Tremaine 2002[43]). The relative risk of remission (CDAI<150) at 8 weeks was 1.96 (95%CI: 1.19 to 3.23);
- budesonide is more effective than mesalamine for induction of remission in active ileo-caecal Crohn's disease. This conclusion was based on a single study of Entocort by Thomsen et al 1998[48] in which the relative risk of remission at 8 weeks was 1.63 (95%CI: 1.23 to 2.16), p=0.0007;
- short term efficacy with budesonide is less than with conventional steroids, particularly in patients with severe disease or more extensive colonic involvement (however, the likelihood of adverse events and adrenal suppression was lower). Of note, rather than being pooled, the results for remission rates (CDAI<150) at 8 weeks were presented separately according to whether the budesonide formulation was CIR or pH-dependent:
  - budesonide CIR was inferior to conventional steroids RR = 0.84 (95%CI: 0.71 to 0.98); and
  - there was no statistically significant difference between Budenofalk compared to conventional steroids, RR = 0.87 (95%CI: 0.71 to 1.07), based on papers by Bar-Meir et al 1998 (BUC-23)[91], Gross et al 1996[40] and Levine et al 2003[55]. A sensitivity analysis restricted to good quality studies (Bar-Meir et al 1998[91] (BUC-23) and Gross et al 1996[40]) gave almost identical results RR 0.87 (95%CI: 0.70 to 1.07).

Evaluator's conclusions on clinical efficacy for adult Crohn's disease

Budenofalk oral capsules have been shown to induce remission in adult patients with mild to moderate active Crohn's Disease of the ileum and/or colon in 2 well conducted, randomised, double blinded active comparator controlled studies of 8 weeks duration (Studies BUC-52/CDA and BUC-23). The comparators used in those studies were mesalazine and prednisone, both of which have accepted efficacy in the treatment of this condition.

In Study BUC-52/CDA, Budenofalk was satisfactorily shown to be non-inferior to oral mesalazine in terms of rates of remission (CDAI <150) at 8 weeks. Furthermore, the benefits of Budenofalk in terms of the changes in CDAI observed in this setting can be considered to be clinically important, especially given that more than 70% of the enrolled patients were less than 40 years old when first diagnosed with Crohn's disease (an age below 40 years is a predictor for a disabling course of the disease), more than 25% had a history of surgery due to Crohn's disease and around 12% of the patients suffered from actual or formerly fistulising disease. Thus study also demonstrated comparable remission rates for Budenofalk dosage regimens in (3 mg tid 71.8% versus 9 mg od 67.1%, p=0.5275). Both treatment regimens induced clinically significant reductions in CDAI scores (mean reductions from baseline to final visit (LOCF) of 149.9 and 147.7, respectively) and rates of response (100) were also very similar for the two regimens (76.9% versus 75.0%, respectively).

In Study BUC-23 the rate of clinical response (CDAI <150) at 8 weeks without steroid induced ADRs was twice as high with Budenofalk (30.0% compared with 13.9% for prednisone;, p = 0.004) (ITT analysis). Similar results were observed for the PP analysis set (33.3% versus

[91] Bar-Meir S, Chowers Y, Lavy A, et al and the Israeli Budesonide Study Group. Budesonide versus prednisone in the treatment of active Crohn's disease. *Gastroenterology* 1998; **115(4)**: 835-40.

13.8%, p=0.002), as well as in most subgroup analyses of the effect of Crohn's disease duration, severity, localisation and presence of extra intestinal manifestations.

Although some limitations of the supporting/exploratory data have been identified, clinical remission rates with the proposed dosage regimen for Budenofalk were consistently above 50% across these and the pivotal confirmatory studies.

No data have been submitted to demonstrate the maintenance of remission by Budenofalk.

Safety

Safety in adults

The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy (confirmatory) studies for Crohn's disease (BUC-23, BUC-52/CDA), the following safety data were collected:

- General adverse events (AEs) were either reported spontaneously by the patient, observed by the investigator or elicited by the non-directive question "Has your health worsened since you last saw me?". The date and time of onset, description, intensity, duration and outcome, aetiology, relationship of the adverse event to study drug and action taken were recorded in the CRF. This was assessed at each study visit (baseline, Weeks 2, 4, 6 and 8). AEs were categorised as serious and non serious using the standard ICH definition. The causal relationship between an AE and study medication was classified according to standard WHO criteria.

  Treatment emergent AEs were summarised by body system and by the number and frequency of patients who experienced at least one adverse event within that body system. Similar summary tables were produced for the number and frequency of patients with possibly drug related adverse events, serious adverse events and withdrawals due to adverse events.

- AEs of particular interest in both pivotal studies were steroid related events. Specifically in Study BUC-23, steroid related adverse events was a key component of the primary efficacy outcome and 12 pre defined symptoms and signs known to be associated with glucocorticoid therapies were documented on a dedicated page of the CRF thoughout the study.

- Laboratory tests, comprising standard haematology and biochemistry parameters and urinalysis, were performed at baseline and Weeks 2, 4, 6 and 8 in both studies. (Note glucose levels were not monitored in BUC-52/CDA). The number of patients with low, normal or high laboratory values were summarised for each parameter by treatment group.

- Laboratory tests of particular interest were serum osteocalcin levels in Study BUC-23 and cortisol levels in Sstudy BUC-52/CDA. Serum osteocalcin levels were measured at baseline and the study termination visit in Study BUC-23 and presented by way of summary statistics for both the absolute values and changes from baseline. Serum cortisol levels were measured at each visit in Study BUC-52/CDA. Absolute serum cortisol levels, changes from baseline and the proportion of patients with cortisol deteriorations (either above or below normal range) were measured to assess the degree of adrenal and pituitary suppression.

- Vital signs (blood pressure, pulse and body weight) were tabulated at each visit and the change from baseline was summarised.

- A global assessment of tolerability by patient and investigator at the final/withdrawal examination.

In the pivotal study for collagenous colitis (BUC-35), the following safety data were collected:

- General adverse events (AEs) were reported spontaneously by the patient and assessed at Weeks 2, 4 and 8 during double blind treatment and at Wweeks 12 and 16 during open label treatment. Patients instructed to contact the investigator if any serious or unexpected AE occurred. An unexpected AE was an event that was not identified in nature, severity, or frequency in the current product information sheet.
- Vital signs (pulse rate, blood pressure and body weight) and physical examination assessed at Weeks 0 and 8 during double blind treatment and at Weeks 12 and 16 during open label treatment and body weight additionally at Weeks 2 and 4.

Of particular note: in Study BUC-35 there was no assessment of causal relationship of adverse events to study medication except for serious AEs; and laboratory parameters were not monitored.

Dose response and non pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- Study BUF-15/CDA presented AE data at Weeks 3, 6 and 12 (final visit), as well as ADRs associated with previous steroid treatment for Stratum 2 at baseline and Wweeks 3 and 6. AEs were elicited and assessed for causality in the same manner as in the pivotal confirmatory studies. Laboratory parameters were restricted to standard haematology, CRP and ESR, glucose, ALT, γGT and alkaline phosphatase and serum cortisol. These were assessed at baseline and Weeks 3, 6 and 12 and presented by way of absolute and percentage changes from baseline and frequency of abnormal results.
- Study BUF-16/CDA presented data on adverse events at Days 14 ± 3, 28 ± 7, 42 ± 7 and 56 ± 7, and at follow up after dose reduction for 14 days (Day 70 ± 7). AEs were elicited and assessed for causality in the same manner as in the pivotal confirmatory studies. The incidence of clinically significant laboratory parameter values (standard haematology and biochemistry) and vital signs were also assessed at each visit,and a global assessment of tolerability by patient and investigator was performed at the end of treatment. (Note: summary data for the standard laboratory parameters were not calculated). Laboratory tests of particular interest were serum cortisol levels (measured at baseline and Days 14 ± 3, 56 ± 7 and 70 ± 7), with a corticotropin releasing hormone stimulation test stimulation test at baseline and Dday 56 ± 7; and serum osteocalcin (measured at baseline and Day 56 ± 7).
- The two papers published by Gross et al 1996[40] and Caesar et al 1997[41] contained scant safety information. Neither publication reported how AEs were elicited (for example, by directed questioning, questionnaire or spontaneously) nor how the causal relationship to study medication was assessed. Both papers mentioned monitoring of laboratory parameters associated with inflammation and disease activity such as CRP, ESR, haemoglobin and WCC but there was no mention of monitoring of other standard haematology and biochemistry parameters and no indication as to whether cortisol or osteocalcin levels etc had been monitored.

Other studies evaluable for safety only

Study BUC-44/LMC

This randomised, double blind, placebo controlled, multi centre study compared Budenofalk 3 mg capsules and placebo in the treatment of lymphocytic colitis. Patients with an established diagnosis of lymphocytic colitis were randomised to treatment with either Budenofalk 9 mg od

(n=21) or placebo (n=21) for 6 weeks (double blind period). Thereafter, non responders were treated with Budenofalk for another 6 weeks (open label period). The study provided AE and ADR data at 3 and 6 weeks during double-blind treatment and at 9 and 12 weeks during the open-label period and tolerability assessments 6 and 12 weeks. Assessment of vital signs and physical examination were performed at baseline only. Laboratory parameters were not monitored.

Clinical pharmacology studies

Adverse events were monitored in all of the clinical pharmacology studies. Participants were asked about possible adverse events in a non suggestive manner and these and any adverse events observed by the investigator were documented on Case Report Forms. However, because so few AEs were reported in the clinical pharmacology studies they were usually not analysed for a causal relationship with the study medication.

There was an inconsistent approach to the monitoring of changes in haematology and biochemistry parameters during the course of these studies:

- there was no pre and post monitoring for assessment of changes in laboratory parameters in Studies BUC-5.C3, BUC-5.C9/BIO and BUC-5.C18/BIO and BUC-14/BIO;
- in Studies BUC-5.C3 NBF_BF, BUC-5.C9 NBF_BF and Kolkman et al 2004[37], only white cell counts and plasma cortisol were monitored and these were part of the pharmacodynamic investigations;
- in Study BUC-59/BIO clinical chemistry data were only obtained at screening, whilst haematology and coagulation parameters were measured at screening and 14 days after budesonide administration; and
- in the study by Hempfling et al 2003[38], effects on cortisol production and urinary excretion, liver function, immunoglobulin M and lymphocyte and neutrophil counts were assessed as part of the pharmacodynamic investigation.

Similarly, changes in vital signs were assessed in only a subset of the studies ; BUC-59/BIO, BUC-5.C3 NBF_BF and BUC-5.C9 NBF_BF and BUC-48/BIO.

Pivotal studies that assessed safety as a primary outcome

Nil studies submitted.

Patient Exposure

A total of 858 adults were exposed to Budenofalk oral capsules in the studies submitted, with 114 participating in the clinical pharmacology program, 684 in Phase II and III studies of adults Crohn's disease and 60 in studies used to support the withdrawn indication for collagenous colitis (Table 53). Overall, there were 68 were healthy volunteers; 696 patients with active Crohn's disease; 26 patients with collagenous colitis; 34 patients with lymphocytic colitis; 15 patients with ulcerative colitis and 19 patients with primary biliary cirrhosis.

A total of 670 individuals received the recommended 9 mg daily dose of Budenofalk; 181 via a once daily regimen and 489 via a divided dose regimen (3 mg tid). All patients suffering from collagenous (and lymphocytic) colitis received a once daily dose of Budenofalk, whereas the majority of Crohn's disease patients received Budenofalk in a divided dose regimen.

The recommended duration of treatment proposed in the draft PI is 8 weeks. Treatment for 8 or more weeks occurred in 463/670 (69.1%) individuals exposed to Budenofalk and a further 123/670 (18.4%) were exposed for between 6 and 8 weeks (Table 54). The highest and longest exposure occurred in the two dose ranging studies in patients with Crohn's disease. In Study

BUC-15/CDA, 33 patients were treated with 9 mg Budenofalk per day for up to 12 weeks. In Study BUC-16/CDA, 104 patients received 9 mg daily for 8 weeks, followed by 6 mg daily for a further 2 weeks. In both these studies a further 32 and 99 patients respectively, were exposed to 18 mg Budenofalk daily for the same periods.

Table 53. Exposure of adults to Budenofalk and comparators in clinical studies

	Controlled studies					Uncontrolled studies	Total BUC
	BUC	Placebo	Mesalazine	Prednisone	6-MPred		
Clinical pharmacology							
Healthy volunteers						68	68
Patients							
Crohn's disease						12	12
PBC						19	19
Collagenous colitis							0
Ulcerative colitis	15 @						15
Subtotal pharmacology	***15 @***					***99***	***114***
Crohn's disease							
Pivotal	254		153	101			254
Supporting study	34				33	89	123
Dose-finding study	307	102					307
Subtotal Crohn's disease	***595***	***102***	***153***	***101***	***33***	***89***	***684***
Collagenous colitis							
Pivotal	26 *	14					26*
Supporting study							
Lymphocytic colitis	*34 ^*	*21*					*34^*
Dose-finding study							0
Subtotal Collagenous colitis	***60 *^***	***35***					***60***

	Controlled studies					Uncontrolled studies	Total BUC
	BUC	Placebo	Mesalazine	Prednisone	6-MPred		
TOTAL	670 *^	137	153	101	33	188	858

BUC=Budenofalk oral capsules, EOC=Entocort oral capsules, 6-MPred=6-Methylprednisolone

* includes 11 of 14 placebo patients who received Budenofalk during open-label phase of BUC-35

^ includes 13 of 21 placebo patients who received Budenofalk during an open-label phase of BUC-44/LMC

@ study was “controlled” only in the sense that there were two dosage groups but no other active comparator or placebo

Table 54. Exposure of adults to Budenofalk in clinical studies according to dose and duration.

	Daily Dose range						Duration of BUC treatment at 9 mg daily			
	0mg	3 mg	6mg	9 mg 9 mg od	3 mg tid	18mg	< 1 wk single or multi-dose	1-4 wks	6-<8 wks	≥ 8 wks
Clinical pharmacology										
Healthy volunteers		12*		38**	12	6	50			
Adults										
Crohn's disease					12^					12^
PBC		19@	19@		19@			19		
Collagenous colitis										
Ulcerative colitis				7	8		15			
Adult Crohn's disease										
Placebo-controlled	102$	104$			104$	99$				104
Active-controlled				76	212					288
Uncontrolled			39		122#	32			89	33

	Daily Dose range						Duration of BUC treatment at 9 mg daily			
	0mg	3 mg	6mg	9 mg 9 mg od	3 mg tid	18mg	< 1 wk single or multi-dose	1-4 wks	6-<8 wks	≥ 8 wks
Collagenous colitis										
Placebo-controlled	14			26[&]						26[&]
Active-controlled										
Uncontrolled										
Lymphocytic colitis										
Placebo-controlled	21			34[$$]					34[$$]	
Active-controlled										
Uncontrolled										
TOTAL	137	135	58	181	489	137	65	19	123	463

*=12 volunteers received a single 3 mg dose in fasting and fed state 1 week apart; ** =12 volunteers received a single 9 mg dose in fasting and fed state 1 week apart; ^=12 patients in BUC-14/BIO had been enrolled in studies BUC-2 or BUC-9 and continued to take medication for at least a week and then PK profiling over a 24 h period was performed; [@ =]this study was a dose-escalation study in which the same 19 patients received 3, 6 and 9 mg daily for one week at a time; $=BUC-16/CDA patients receiving placebo and 3 mg BUC for 8 weeks then rece9ved placebo for 2 weeks and patients receiving 9 and 18 mg for 8 weeks then received 6 mg daily for 2 weeks; #=44 of 89 patients in study Caesar et al 1997 who achieved remission also received 6 mg for additional 6 weeks; &=includes 11 placebo patients who received open label BUC for 8 weeks; $$=includes 13 placebo patients who received open label BUC for 6 week

Adverse Events

All adverse events (irrespective of relationship to study treatment)

Adult Crohn's disease

Pivotal studies

In Study BUC-23, 66.0% patients in the Budenofalk group and 66.3% patients in the Prednisone treatment group reported at least one adverse event during the study course. The most common affected body systems were the gastrointestinal system (approximately 42% patients in each treatment group); General disorders (21% BUC; 28% Pred); Musculo-skeletal system (20% BUC; 13.9% Pred); Skin and appendages (16% BUC; 10.9% Pred); and the Nervous system (10% BUC; 11.9% Pred). The most common single events were abdominal pain (21% BUC; 15.8% Pred), diarrhoea (12% BUC; 6.9% Pred), epigastric pain/upper abdominal pain (4% BUC; 9.9% Pred), headache (5% BUC, 7.9% Pred), asthenia (5% BUC; 6.9% Pred), fatigue (6% BUC; 5.9% Pred) and arthalgia (8% BUC; 4% Pred).

AE rates somewhat lower in Study BUC-52/CDA, with at least one treatment emergent AE being recorded for 47.1% patients in the mesalazine group, 46.8% patients in the BUC 9 mg od group and 39.2% in the BUC 3 mg tid group. Most AEs were gastrointestinal disorders, infections and infestations, or nervous system disorders. The rate of Gastrointestinal disorders differed considerably between the total BUC group and mesalazine (14.1% versus 24.2%). This was explained by the fact that exacerbation and symptoms of Crohn's disease had to be reported as an AE in the SOC "Gastrointestinal disorders", with the different rates in Gastrointestinal disorders most likely reflecting the efficacy results. The most common AEs were: headache (BUC 3 mg tid 7.6%; BUC 9 mg od 10.4%; mesalazine 12.4%); viral infection (BUC 3 mg tid 3.8%; BUC 9 mg od 10.4%; mesalazine 3.3%); Crohn's disease (BUC 3 mg tid 6.3%; BUC 9 mg od 3.9%; mesalazine 7.8%); vomiting (BUC 3 mg tid 3.8%; BUC 9 mg od 0%; mesalazine 3.9%); abdominal pain (BUC 3 mg tid 1.3%; BUC 9 mg od 2.6%; mesalazine 5.2%); back pain (BUC 3 mg tid 2.5%; BUC 9 mg od 3.9%; mesalazine 0.7%); pyrexia (BUC 3 mg tid 3.8%; BUC 9 mg od 1.3%; mesalazine 3.3%) and blood cortisol decreased (BUC 3 mg tid 5.1%; BUC 9 mg od 3.9%; mesalazine 0%)

Other studies

In Study BUC-15/CDA, AEs were reported in 81/108 (75.0%) patients in the 2 mg tid budesonide group, in 79/99 (79.8%) patients of the 3 mg tid budesonide group and in 88/106 (83.0%) of patients in the 6 mg tid budesonide group. The most common events were headache (increasing in frequency with increasing dose; 29.6%, 32.3% and 35.8% patients, respectively), flu like illness, upper respiratory tract infections (URTI) and abdominal pain.

Headache was also the most commonly reported AE in Study BUC-16/CDA, although the rates were at a much lower level than in Study BUC-15/CDA (4% in the placebo group and 7-9% in the active treatment groups, without any dose dependent increase). The overall rate of AEs was also lower in Study BUC-16/CDA than in Study BUC-15/CDA; AEs reported for 32/102 (31.4%) patients in the placebo group and 36/104 (34.6%), 42/104 (40.4%) and 38/99 (38.4%) patients in the budesonide 3 mg, 9 mg and 18 mg treatment groups, respectively. Other commonly reported adverse events were infection, nausea, vomiting, abdominal pain and increased appetite.

Gross et al 1996[40] reported that 11 patients in the BUD group (31.4%, 95% CI: 16.9% - 49.3%) and 24 patients in the 6-methylprednisolone group (72.7%, 95% CI: 54.5% - 86.7%) had at least one side effect. Individual AEs were not identified. However, it was reported that most AEs were either dermatological (such as acne or moon face) or behavioural/neurological/psychiatric (such as restlessness and disturbed sleep) in nature.

Caesar et al 1997[41] reported that 22.5% of patients who received 9 mg daily for 6 weeks had an AE. Individual AEs were not identified but there was a statement that there were no cases of insomnia or moon face. During the second phase of treatment with 6 mg daily for 6 weeks, 11.4% of patients reported an AE.

In the clinical pharmacology studies, AEs were reported as follows:

- Studies BUC-5.C3 NBF_BF, BUC-5.C9 NBF_BF, BUC-5.C9/BIO & BUC-5.C18/BIO and BUC-14/BIO : nil AEs;
- BUC-5.C3 (n=1): a case of conjunctivitis with onset 2 days after study completion, thought not to be causally related to treatment;
- BUC-59/BIO (n=2): mild reflux oesophagitis, which started about 9 days after budesonide intake and lasted for 12 days; and a report of headache of moderate intensity, which started about 17 days after budesonide intake and lasted for 12 h;
- Hempfling et al 2003 3 (n=5; all reported as ADRs): 3 ADRs were reported by 2 patients with Stage I/II PBC (all non serious; transient dizziness, blurred vision, hot flushes). Three patients with Stage IV PBC also had an ADR. One developed weight gain, ankle oedema, sleeplessness and ascites. Two patients developed portal vein thombosis in close temporal relationship with administration of budesonide; both had significantly increased peak plasma levels of budesonide and decreased clearances from plasma; and
- Kolkman et al 2004 (n=5): 5 AEs in 5/15 (33%) ulcerative colitis patients (2 receiving 3 mg tid and 1 receiving 9 mg od), all reported as mild with gastrointestinal distress in 3 and nervousness and ankle oedema in one each (note ADRs were said to have occurred in 3 patients (1 in the 3 mg tid group and 2 in the 9 mg od group) but the reactions weren't stated.

Evaluator's comment

The adverse event rate varied considerably across the studies submitted. The highest rates were observed in Studies BUC-23 and BUC-15/CDA where in excess of 65% patients in all treatment groups reported AEs. These studies were not placebo controlled and in both studies there was a particular focus on steroid induced events, which is likely to have resulted in a degree of "stimulated reporting". Study BUC-23 incorporated the steroid reactions as part of the primary study outcome and used a CRF specially dedicated for the recording of such events. In Study BUC-15/CDA, one of the aims of the study was to determine the most appropriate dose of Budenofalk for steroid dependent patients. Thus, there was a focus on both ADRs existing at the time of study enrolment and the worsening of existing and emergence of new steroid ADRs during the course of the study. The number of adverse and serious adverse events reported in Study BUC-16/CDA was relatively low compared to the other blinded studies. This study was mainly conducted in Russia and the difference may partly be due to different geographical and cultural factors. The lowest AE rate occurred in the open, uncontrolled study by Caesar et al 1997, where only 22.5% patients were reported to have experienced an AE.

Table 55, summarises the AE data from the confirmatory and exploratory studies, showing the rates of events that occurred in ≥5% in at least one treatment arm in any of the studies. The shading indicates those treatment arms in which patients received the proposed Budenofalk dosage regimen of 3 mg tid for 8 weeks. Most of the AEs can be classified into 2 broad groups; those that can be attributed to the underlying disease (such as abdominal pain, fever, diarrhoea, flatulence, Crohn's disease etc) and those recognised as being associated with steroid therapy (for example, acne, depression, sleeplessness, Cushing's syndrome, increased appetite, infection etc).

Table 55. Adverse events reported in ≥ 5% patients in at least one treatment arm of any study conducted in adult Crohn's patients. Table continued across three pages.

	Confirmatory studies					Exploratory studies									
	BUC-23		BUC-52/CDA			BUC-15/CDA			BUC-16/CDA				Gross et al 1996		Caesar
	BUC 3mg tid	Pred	BUC 3mg tid	9mg od	Mes 500mg tid	BUC 2mg tid	3mg tid	6mg tid	Placebo	BUC 1mg tid	3mg tid	6mg tid	BUC 3mg tid	6-Methyl Pred	BUC 3mg tid →2mg tid
Total daily dose	9mg	Taper	9mg	9mg	4.5g	6mg	9mg	18mg	0	3mg	9mg	18mg	9mg	Tapered	9 → 6mg
Durat'n	8wks	8wks	8wks	8wks	8wks	12wks	12wks	12wks	8wks	8wks	8wks	8wks	8wks	8wks	6 + 6wk
Safety pop'n N	100	101	79	77	153	108	99	106	102	104	104	99	34	33	89
Any AE	**66%**	**66.3%**	**39.2%**	**46.8%**	**47.1%**	**75.0%**	**79.8%**	**83.0%**	**31.4%**	**34.6%**	**40.4%**	**38.4%**	**31.4%**	**72.7%**	**22.5%**
Cushing's syn.	0	0	0	0	0	0.9%	0	6.6%	0	0	<1%	5%			
↓ s. cortisol	NM	NM	5.1%	3.9%	0	NR	NR	NR	NR	NR	NR	NR			
swelling	2%	5.0	0	0	0	2.8	2.0	0.9	0	0	<1%	0			

	Confirmatory studies					Exploratory studies									
	BUC-23		BUC-52/CDA			BUC-15/CDA			BUC-16/CDA				Gross et al 1996		Caesar
	BUC 3mg tid	Pred	BUC 3mg tid	9mg od	Mes 500mg tid	BUC 2mg tid	BUC 3mg tid	BUC 6mg tid	Placebo	BUC 1mg tid	BUC 3mg tid	BUC 6mg tid	BUC 3mg tid	6-Methyl Pred	BUC 3mg tid →2mg tid
face/ext		%				%	%								
abdo pain	21 %	15.8 %	1.3 %	2.6 %	5.2%	9.3 %	5.1 %	2.8 %	3%	3%	<1%	7%			
abdo pain upper	4%	9.9 %	2.5 %	0	2.6%	0.9 %	0	4.7	0	0	0	0			
appetite ↑	0	3%	0	0	0	0	1.0 %	0.9	4%	<1%	3%	3%			
colic abdo	0	0	0	0	0	2.8 %	1.0 %	6.6	0	0	0	0			
Crohn's disease	0	0	6.3 %	3.9 %	8.5%	0	0	0	0	0	0	0			
diarrhoea	12 %	6.9 %	0	1.3 %	0.7%	3.7 %	5.1 %	0.9 %	2%	<1%	0	1%			
flatulence	4%	5%	1.3 %	1.3 %	0.7%	0	0	0	0	2%	0	2%			

	Confirmatory studies					Exploratory studies									
	BUC-23		BUC-52/CDA			BUC-15/CDA			BUC-16/CDA				Gross et al 1996		Caesar
	BUC 3mg tid	Pred	BUC 3mg tid	9mg od	Mes 500mg tid	BUC 2mg tid	BUC 3mg tid	BUC 6mg tid	Placebo	BUC 1mg tid	BUC 3mg tid	BUC 6mg tid	BUC 3mg tid	6-Methyl Pred	BUC 3mg tid →2mg tid
heartburn	2%	6.9%	0	0	0	1.9%	1.0%	1.9	0	0	0	0			
nausea	7%	0	0	0	2.0%	0.9%	3.0%	6.6%	3%	4%	4%	5%			
vomiting	4%	2%	3.8%	0	3.9%	2.8%	2%	2.8%	2%	<1%	4%	5%			
asthenia	5%	6.9%	0	0	0	0	1.0%	0.9	0	2%	2%	0			
fatigue	6%	5.9%	1.3%	1.3%	0.7%	0	0	0.9	0	0	0	0			
pyrexia	5%	4.0%	3.8%	1.3%	3.3%	4.6%	4.6%	0	3%	3%	<1%	0			
flu-like illness	0	0	0	0	0	12.0%	16.2%	7.5	<1%	<1%	2%	1%			

	Confirmatory studies					Exploratory studies									
	BUC-23		BUC-52/CDA			BUC-15/CDA			BUC-16/CDA				Gross et al 1996		Caesar
	BUC 3mg tid	Pred	BUC 3mg tid	9mg od	Mes 500mg tid	BUC 2mg tid	3mg tid	6mg tid	Placebo	BUC 1mg tid	3mg tid	6mg tid	BUC 3mg tid	6-Methyl Pred	BUC 3mg tid →2mg tid
infection	0	0	0	0	0	0	2%	1.9	4%	4%	5%	7%			
URTI	1%	0	1.3%	0	0.7%	5.6%	4.0%	8.5%	0	0	0	0			
viral infection	0	0	3.8%	10.4%	3.3%	0	0	0.9	0	0	0	0			
arthralgia	8%	4%	1.3%	0	0.7%	2.8%	3.0%	5.7	<1%	2%	3%	1%			
back pain	0	5.0%	2.5%	3.9%	0.7%	4.6%	2.0%	1.9%	<1%	4%	0	3%			
myalgia	4%	3%	0	0	0	0.9%	0	0	3%	0	0	2%			
muscle cramps	6%	3%	0	1.3%	0	0.9%	2%	1.9	0	0	0	0			
headache	5%	7.9	7.6	10.4	12.4	29.6	32.3	35.8	4%	8%	9%	7%			

	Confirmatory studies					Exploratory studies									
	BUC-23		BUC-52/CDA			BUC-15/CDA			BUC-16/CDA				Gross et al 1996		Caesar
	BUC 3mg tid	Pred	BUC 3mg tid	9mg od	Mes 500mg tid	BUC 2mg tid	3mg tid	6mg tid	Placebo	BUC 1mg tid	3mg tid	6mg tid	BUC 3mg tid	6-Methyl Pred	BUC 3mg tid →2mg tid
		%	%	%	%	%	%	%							
sleeplessness	2%	5%	0	0	0	0	2%	0.9	<1%	0	<1%	1%			
acne	5%	4%	0	1.3%	0	3.7%	3.0%	3.8%	0	<1%	<1%	2%			
palpitations	2%	5.9%	0	0	0	0.9%	0	0	0	0	0	0			
hypertension	0	0	0	0	0.7%	0	0	0	2%	2%	5%	6%			

NM not measured. NR not recorded - although cortisol levels were measured, changes above or below the normal range were not recorded as AEs or ADRs

Collagenous colitis

Pivotal studies

In Study BUC-35, 8/15 (53.3%) patients receiving Budenofalk and 8/14 (57.1%) receiving placebo experienced an adverse event. During the double-blind period the most common AEs amongst patients receiving Budenofalk were Nervous system disorders (n=4), whereas in the placebo group the most commonly reported AEs were Gastrointestinal disorders (n=3). The most common individual events were headache (BUC n=3); abdominal pain (Placebo n=2) and cough (BUC n=2).

Other studies

In Study BUC-44/LMC, 3/21 patients (14.3%) in the Budenofalk group and 4/21 patients (19.0%) in the placebo group experienced at least one AE during the course of the study, including 2/21 (9.5%) in the Budenofalk group and 3/21 (14.3%) in the Placebo group during the double blinded period. During open label treatment with budesonide, 2/19 (10.5%) patients reported AEs (one patient with dyspepsia, who had received also budesonide in the double blind phase and one patient with headache who had received placebo in the double blind phase). Most patients experienced Gastrointestinal disorders and Nervous system disorders.

Treatment-related adverse events (adverse drug reactions)

Crohn's disease

Adverse drug reactions are summarised in Table 56, which show those reactions occurring in 3 or more patients in any treatment arm in any study.

Pivotal studies

In Study BUC-23, steroid related adverse events were a key component of the primary efficacy outcome and 12 pre defined symptoms and signs known to be associated with glucocorticoid therapies were documented on a dedicated page of the CRF thoughout the study. The proportions of patients in each group exhibiting these features at each visit are summarised in Table 57. Most of these steroid related features were present in at least some of the patients at baseline. The proportion of patients exhibiting moon face, acne and buffalo hump increased during the study, with the increase being much more marked in the prednisone group than the BUC group. The proportion of patients with hirsutism also increased in the prednisone group but not in the BUC group. The rates of other features either remained stable or decreased during the course of the study, suggesting they are less specific for steroid intake. A comparison of the 5 symptoms which appeared to be most closely steroid related (moon face, acne, buffalo hump, hirsutism and skin striae) showed a significantly lower frequency for Budenofalk than with prednisone (44% versus 67%; p = 0.0018, two-sided Fisher's exact test).

Table 56. Adverse drug reactions reported in 3 or more adult patients with Crohn's disease in at least one treatment arm of any study. Table continued across two pages.

	Confirmatory studies					Exploratory studies									
	BUC-23		BUC-52/CDA			BUC-15/CDA			BUC-16/CDA				Gross et al 1996		Caesar
	BUC 3mg tid	Pred	BUC 3mg tid	9mg od	Mes 500 mg tid	BUC 2mg tid	3mg tid	6mg tid	Placebo	BUC 1mg tid	3 mg tid	6mg tid	BUC 3mg tid	6-MethylPred	BUC 3mg tid →2 mg tid
Total daily dose	9mg	Taper	9mg	9mg	4.5g	6mg	9mg	18mg	0	3mg	9mg	18 mg	9mg	Tapered	9 → 6mg
Durat'n	8wks	8wks	8wks	8wks	8wks	12wks	12wks	12wks	8wks	8wks	8wks	8wks	8wks	8wks	6 + 6wk
Safety pop'n N	100	101	79	77	153	108	99	106	102	104	104	99	34	33	89
Any ADR	**50 %**	**53.5 %**	**10.1 %**	**11.7 %**	**7.2 %**	**31.5 %**	**37.4 %**	**42.5 %**	**12.0 %**	**10.0 %**	**13 %**	**19 %**	**28.6 %**	**69.7%**	**18 %**
Cushing's syn.	0	0	0	0	0	0.9 %	0	6.6 %	0	0	<1 %	5%			
↓ s. cortisol	NM	NM	3.8 %	3.9 %	0	NR	NR	NR	NR	NR	NR	NR			

	Confirmatory studies					Exploratory studies									
	BUC-23		BUC-52/CDA			BUC-15/CDA			BUC-16/CDA				Gross et al 1996		Caesar
	BUC 3mg tid	Pred	BUC 3mg tid	BUC 9mg od	Mes 500 mg tid	BUC 2mg tid	BUC 3mg tid	BUC 6mg tid	Placebo	BUC 1mg tid	BUC 3 mg tid	BUC 6mg tid	BUC 3mg tid	6-MethylPred	BUC 3mg tid →2 mg tid
face swelling	1%	4%	0	0	0	2.8 %	2.0 %	0.9 %	0	0	0	0			
abdo pain	10 %	5.9 %	0	1.3 %	0	0.9 %	0	0	<1%	<1%	0	2%			
abdo pain upper	3%	6.9 %	0	0	1.3 %	2.8 %	0	0	0	0	0	0			
appetite ↑	0	3.0 %	0	0	0	0	1.0 %	0.9 %	4%	<1%	3%	2%			
flatulence	2%	3.0 %	1.3 %	1.3 %	0	0	0	0	0	<1%	0	1.0 %			
asthenia	3%	6.9 %	0	0	0	0	1.0 %	0.9 %	0	<1%	0	0			
myalgia	4%	3%	0	0	0	0.9 %	0	0	<1%	0	0	1%			

	Confirmatory studies					Exploratory studies									
	BUC-23		BUC-52/CDA			BUC-15/CDA			BUC-16/CDA				Gross et al 1996		Caesar
	BUC 3mg tid	Pred	BUC 3mg tid	9mg od	Mes 500 mg tid	BUC 2mg tid	BUC 3mg tid	BUC 6mg tid	Placebo	BUC 1mg tid	3 mg tid	6mg tid	BUC 3mg tid	6-MethylPred	BUC 3mg tid →2 mg tid
muscle cramps	4%	3%	0	0	0	0.9 %	2.0 %	1.9 %	0	0	0	0			
depression	0	3.0 %	0	0	0	0	1.0 %	1.9 %	0	0	<1 %	0			
headache	5%	6.9 %	2.5 %	1.3 %	0	29.6 %	31.3 %	34.9 %	<1%	0	3%	2%			2.2 %
insomnia	2%	5.0 %	0	0	0	1.9 %	2.0 %	0	<1%	0	<1 %	1%			
menstrual irreg	0	2.0 %	0	0	0	1.9 %	3.0 %	1.9 %	0	0	0	2%			2.2 %
acne	5%	4%	0	1.3 %	0	3.7 %	3.0 %	3.8 %	0	<1%	<1 %	2%			1.1 %
hypertension	0	0	0	0	0	0	0	0	<1%	<1%	3%	2%			

NM=not measured; NR=not recorded; although cortisol levels were measured, changes above or below the normal range were not recorded as AEs or ADRs

Table 57. Steroid-related events, study BUC-23

Budesonide, n = 100

symptom	visit 1; n (%)	visit 2; n (%)	visit 3; n (%)	visit 4; n (%)	visit 5; n (%)
moon face	6 (6.0)	9 (9.0)	16 (16.0)	17 (17.0)	16 (16.0)
acne	15 (15.0)	14 (14.0)	19 (19.0)	22 (22.0)	19 (19.0)
mood changes	27 (27.0)	22 (22.0)	16 (16.0)	9 (9.0)	10 (10.0)
headache	17 (17.0)	20 (20.0)	19 (19.0)	11 (11.0)	9 (9.0)
muscle weakness	30 (30.0)	22 (22.0)	17 (17.0)	10 (10.0)	10 (10.0)
dyspepsia	25 (25.0)	21 (21.0)	16 (16.0)	12 (12.0)	10 (10.0)
vertigo	20 (20.0)	11 (11.0)	16 (16.0)	5 (5.0)	8 (8.0)
swollen ankles	7 (7.0)	7 (7.0)	6 (6.0)	6 (6.0)	6 (6.0)
buffalo hump	1 (1.0)	2 (2.0)	0 (0.0)	4 (4.0)	2 (2.0)
hirsutism	5 (5.0)	1 (1.0)	3 (3.0)	3 (3.0)	2 (2.0)
skin striae	3 (3.0)	1 (1.0)	1 (1.0)	2 (2.0)	3 (3.0)
easy bruising	1 (1.0)	1 (1.0)	2 (2.0)	1 (1.0)	0 (0.0)

Prednisone, n = 101

symptom	visit 1; n (%)	visit 2; n (%)	visit 3; n (%)	visit 4; n (%)	visit 5; n (%)
moon face	5 (5.0)	21 (20.8)	34 (33.7)	43 (42.6)	33 (32.7)
acne	13 (12.9)	15 (14.9)	26 (25.7)	27 (26.7)	29 (28.7)
mood changes	29 (28.7)	25 (24.8)	20 (19.8)	17 (16.8)	16 (15.8)
headache	11 (10.9)	10 (9.9)	11 (10.9)	12 (11.9)	12 (11.9)
muscle weakness	26 (25.7)	15 (14.9)	11 (10.9)	11 (10.9)	10 (9.9)
dyspepsia	30 (29.7)	15 (14.9)	14 (13.9)	12 (11.9)	8 (7.9)
vertigo	16 (15.8)	9 (8.9)	10 (9.9)	9 (8.9)	5 (5.0)
swollen ankles	9 (8.9)	8 (7.9)	11 (10.9)	11 (10.9)	6 (5.9)
buffalo hump	2 (2.0)	5 (5.0)	5 (5.0)	10 (9.9)	10 (9.9)
hirsutism	3 (3.0)	5 (5.0)	4 (4.0)	7 (6.9)	8 (7.9)
skin striae	5 (5.0)	4 (4.0)	1 (1.0)	5 (5.0)	2 (2.0)
easy bruising	- (-)	4 (4.0)	5 (5.0)	5 (5.0)	2 (2.0)

In Study BUC-52/CDA, 7.2% patients in the mesalazine group and 10.9% in the combined BUC group experienced at least 1 ADR. There was no difference between the BUC 3 mg tid and 9 mg od dosage regimens in the ADR rate (10.1% and 11.7%, respectively). The most commonly affected SOCs were the Gastrointestinal system (total BUC 2.6%, mesalazine 5.2%), Investigations (total BUC 5.1%; mesalazine 2.0%) and Nervous system disorders (total BUC 1.9%; mesalazine nil). The most common individual ADRs with Budenofalk were decreased serum cortisol (n=6 (3.8%)), headache (n=3 (1.9%)) and flatulence (n=2 (1.3%)). Other ADRs, all n=1, were: leucocytosis, leucopenia, abdominal pain, diarrhoea, dyspepsia, hepatic function abnormal, hepatic enzyme increased, haematuria and acne. The most common ADRs with mesalazine were upper abdominal pain, pancreatitis and vomiting (all n=2 (1.3%)). Other ADRs for this group (all n=1), were: abdominal distension, diarrhoea, hepatic function abnormal, blood amylase increased, lipase increased, transaminases increased, International Normalized Ratio (INR)[92] increased, musculoskeletal pain, pain in jaw and allergic dermatitis. Known side effects of mesalazine are hypersensitivity reactions such as pancreatitis and allergic skin reaction, musculoskeletal pain (myalgia, arthalgia) and changes in the hepatic function.

[92] The prothrombin time (PT) and its derived measures of prothrombin ratio (PR) and international normalized ratio (INR) are measures of the extrinsic pathway of coagulation. This test is also called "ProTime INR" and "INR PT". They are used to determine the clotting tendency of blood, in the measure of warfarin dosage, liver damage, and vitamin K status. PT measures factors I (fibrinogen), II (thrombin), V, VII, and X. It is used in conjunction with the activated partial thromboplastin time (aPTT) which measures the intrinsic pathway. The INR in absence of anticoagulation therapy is 0.8-1.2. The target range for INR in anticoagulant use (e.g. warfarin) is 2 to 3.

Other studies

In Study BUC-15/CDA, two sets of ADR results were presented; those according to the trial investigators' assessment and those according to the Director of the Clinical Trial's assessment of individual AEs. According to the investigators, 31.5% patients in the BUC 6 mg group, 37.4% of patients in BUC 9 mg group and 42.5% patients in 18 mg group had at least one ADR. This was suggestive of a dose response relationship, however no statistically significant differences in any of the AE or ADR rates were found in the intergroup comparisons. The most commonly reported ADRs were Cushing's syndrome, headache, acne, face swelling and menstrual irregularities.

According to the Director of the Clinical Trial, the proportion of patients with at least one possible ADR was 60% in the BUC 6 mg budesonide group, 72% in the BUC 9 mg group and 73% in the BUC 18 mg group. At least one *typical* steroid-induced ADR occurred in 21% of patients in the 6 mg BUC group, 16% in the 9 mg BUC and in 25% in the 18 mg BUC group. The typical steroid induced ADR "Cushing's syndrome" occurred, or worsened if it was already present at enrolment in the trial, almost exclusively with BUC daily doses of 18 mg, whereas steroid induced ADRs affecting the skin (such as acne) were often reported in all three treatment groups.

It should be noted these results for Study BUC-15/CDA are for Strata 1 and 2 combined. Newly occurring ADRs in patients from Stratum 1 (no recent steroid therapy) were mostly reported in a single patient at any follow-up visit. The ADRs occurring in 2 or more patients were headache (most commonly reported for all dosage groups with no apparent dose dependency), "stomach upset" (all treatment groups), influenza like symptoms (most commonly reported in the BUC 9 mg group) and acne/acneiform dermatitis (6 mg and 18 mg groups) and Cushing's syndrome (18 mg group only). Of some note, the switch from systemic steroids to budesonide did not result in an overall lower number of patients being affected by typical steroid side effects in any group. However, the occurrence of Cushingoid symptoms was reduced, especially with the 6 mg and 9 mg daily dosage regimens.

The most commonly reported ADRs in Study BUC-16/CDA were Cushing's syndrome, headache, increased appetite (the highest rate was in the placebo group) and hypertension.

ADRs definitely related to treatment were reported for one patient receiving placebo (allergic reaction, melaena), one patient receiving BUC 3 mg daily (allergic reaction), one patient receiving BUC 9 mg daily; and for two patients receiving BUC 18 mg daily (Cushing's syndrome; increased appetite and peripheral oedema).

Gross et al 1996[40] reported a lower rate of ADRs in the BUC group (28.6%; 95% CI 14.6% - 46.3%) than in the 6-methylprednisolone group (69.7%; 95% CI 51.3% - 84.4%, p=0.0015). Most of the ADRs were either dermatological disorders (acne) or Cushingoid features (moon face). Many patients also complained of behavioural/neurological/psychiatric disorders such as restlessness and disturbed sleep. In the uncontrolled study by Caesar et al 1997[41], ADRs were reported in 16 (18%) patients; abdominal pain (n=3), general complaints/urticaria (n=3), headache (n=2), irregular menses (n=2) and acne, hair loss, abnormal sweating, weight gain, oily taste, polyuria and polydypsia, reddening of skin (all n=1).

Collagenous colitis

Pivotal study

In Study BUC-35 there was no assessment of causal relationship to study medication except for serious AEs (of which there were 2 and neither was considered treatment related). However, one patient in the Budenofalk group developed Cushingoid features and an ecchymosis during the double blind phase of the trial, with the Cushingoid features

persisting into the open label follow-up. A second patient in the Budenofalk group also had Cushingoid features documented at Week 8 but this was not recorded as an AE. By Week 16 these features were said to have disappeared.

Other study

A total of 4 patients (2 from each treatment group) experienced an ADR in Study BUC-44/LMC. ADRs in the placebo group were nausea, abdominal pain and hyperhidrosis in one patient and weight gain in another. In the Budenofalk group, one patient experienced headache and gastro-oesophageal reflux disease and another patientdeveloped a cardiovascular disorder (not otherwise specified (NOS)), fatigue, feeling abnormal and migraine.

Deaths and other serious adverse events (SAEs)

Crohn's disease

Pivotal studies

There were no deaths in either confirmatory study of adult Crohn's disease. A total of 16/201 (8.0%) patients in Study BUC-23 and 9/309 (2.9%) in Study BUC-52/CDA experienced a serious adverse event. Vignettes were provided for all serious AEs. In Study BUC-23 the serious AEs were split evenly between the BUC and prednisone treatment groups and most of the events were described as hospitalisation due to exacerbation or complication of the underlying Crohn's disease (such as abdominal pain, fever, deterioration of anaemia, bloody diarrhoea, ileus). Only 1 of the SAEs was considered by the investigator to be related to the steroid treatment (nausea and vomiting in a prednisone patient).

In Study BUC-52/CDA, 2 patients receiving BUC 3 mg tid and 7 receiving mesalazine were recorded as experiencing a serious AE and in all cases, the reason for classifying the AE as serious was hospitalisation or prolonged hospitalisation. Most of the cases were, again, due to exacerbation or complication of the underlying Crohn's disease (such as abdominal pain, surgery) and not considered related to study medication. Two serious AEs in the mesalazine group were, however, assessed as possibly drug related. In both cases the patients developed pancreatitis which resolved following discontinuation of study medication and supportive therapy.

Other studies

Four deaths were reported in the exploratory studies; 1 in Study BUC-15/CDA and 3 in Study BUC-16/CDA. In Study BUC-15/CDA a patient who received 6 mg daily for 12 weeks suffered a fatal pulmonary embolism 21 days after ending the investigational medication. The pulmonary embolism was assessed as being possibly steroid induced. None of the deaths in Study BUC-16/CDA were considered to be related to the study medication. One patient in the budesonide 18 mg treatment group experienced acute abdominal pain and perforation of the colon on Day 11 of treatment with consequent peritonitis. The patient was hospitalised and study medication was discontinued but the patient died 20 days later. A second patient in the budesonide 18 mg group completed a full course of treatment and was subsequently found to have intestinal carcinoma (reported as an SAE on Day 68). The patient died four months later. The third patient, from the budesonide 3 mg treatment group, discontinued from the study after only two doses of the study medication due to increased abdominal pain and stool frequency. The patient was found to have large intestine perforation and was admitted to hospital but died 24 days later due to purulent peritonitis.

Most SAEs in Study BUC-15/CDA constituted a worsening of their underlying IBD requiring hospitalisation;- 11 (10.2%) patients in the BUC 6 mg group, 7 (7.1%) patients in the BUC 9 mg group and 7 (6.6%) in the BUC 18 mg group. Of note, 2 of the patients in the

BUC 6 mg group were not suffering from Crohn's disease but rather from ulcerative colitis and eosinophilic gastro-enteritis. Serious AEs other than those due to IBD occurred in 1 (0.9%) patient in each of the 6 mg (bilateral leg oedema) and 18 mg (generalised limb pain) BUC groups. The two SAEs in the 9 mg daily group were renal colic and an umbilical hernia with omental incarceration.

In Study BUC-16/CDA, SAEs were reported in 4/102 (3.9%) placebo patients, 3/104 (2.9%) BUC 3 mg patients, 6/104 (5.8%) BUC 9 mg patients and 4/99 (4.0%) BUC 18 mg patients. As in the other dose ranging study, most of the SAEs constituted a worsening or complication of the underlying disease, including ileitis (n=7), large intestine perforation (n=2), intestinal obstruction (n=1), carcinoma (n=1), abdominal pain and bloody diarrhoea (n=1). Thee serious adverse events in two patients were considered to be causally related to treatment; a case of oesophagitis and haemorrhagic gastritis in the BUC 9 mg treatment group and a perforated stomach ulcer (in a patient with a history of peptic ulcer) in the BUC 18 mg treatment group.

There were no deaths reported in the published papers by Gross et al 1996 and Caesar et al 1997. There was no mention of serious AEs in either paper.

Collagenous colitis

Pivotal study

There were no deaths in Study BUC-35 and only 2 serious AEs (1 in each group). In the BUD group a 29 year old was admitted to hospital following an overdose of psychotropic medication, having been diagnosed with depression approximately 2 weeks earlier. This resulted in the patient discontinuing from the study. The AE was not considered to be related to study medication. In the placebo group, a 64 year old was hospitalised with left-sided dysaesthesia, especially in the cervical region and pleuritic pain. No abnormalities were found on lung perfusion scintography and brain magnetic resonance imaging (MRI) and no actual diagnosis was given and the patient subsequently recovered. This was not considered to be related to study medication

Other study

There were no deaths and only 2 serious AEs in Study BUC-44/LMC, both in patients receiving placebo. One 46 year old patient reported nausea, abdominal pain and hyperhidrosis 17 days after commencing treatment and a 62 year old reported headache, neck pain and abdominal discomfort within 2 days of commencing treatment. It is not clear why these events were considered to be serious by the study investigator and it is questionable whether these AEs fulfilled the criteria of a SAE. This was acknowledged in the study report.

Discontinuation due to adverse events

Crohn's disease

Discontinuaitons primarily due to an adverse event occurring in 2 or more patients in any treatment arm in any study are summarised in Table 58.

Table 58. Discontunuations due to an adverse event occurring in 2 or more adult Crohn's patients in any treatment arm of any study. Table continued across two pages.

	Confirmatory studies					Exploratory studies									
	BUC-23		BUC-52/CDA			BUC-15/CDA			BUC-16/CDA				Gross et al 1996		Caesar et al 1997
	BUC 3mg tid	Pred	BUC 3mg tid	9mg od	Mes 500mg tid	BUC 2mg tid	3mg tid	6mg tid	Placebo	BUC 1mg tid	3mg tid	6mg tid	BUC 3 mg tid	6-MethylPred	BUC 3mg tid →2 mg tid
Total daily dose	9mg	Taper	9mg	9mg	4.5g	6mg	9mg	18mg	0	3mg	9mg	18 mg	9mg	Tapered	9 → 6mg
Durat'n	8wks	8wks	8wks	8wks	8wks	12 wks	12wks	12wks	8wks	8wks	8wks	8wks	8wks	8wks	6 + 6wk
Safety pop'n N	100	101	79	77	153	108	99	106	102	104	104	99	34	33	89
Deaths	**0**	**0**	**0**	**0**	**0**	**0.9 %**	**0**	**0**	**0**	**<1 %**	**0**	**2 %**			
Serious AE	**8.0 %**	**7.9 %**	**2.5 %**	**0**	**4.6 %**	**0.9 %**	**2.0 %**	**0.9 %**	**3.9%**	**2.9 %**	**5.8 %**	**4.0 %**			
W/D 2° to	**4.0**	**5.9**	**6.3**	**7.8**	**15.0**	**0^**	**4.0**	**4.7**	**2%**	**4**	**3**	**3**			**2.2**

	Confirmatory studies					Exploratory studies									
	BUC-23		BUC-52/CDA			BUC-15/CDA			BUC-16/CDA				Gross et al 1996		Caesar et al 1997
	BUC 3mg tid	Pred	BUC 3mg tid	9mg od	Mes 500mg tid	BUC 2mg tid	3mg tid	6mg tid	Placebo	BUC 1mg tid	3mg tid	6mg tid	BUC 3mg tid	6-MethylPred	BUC 3mg tid →2mg tid
AE	**%^**	**%^**	**%**	**%**	**%**		**%^**	**%^**		**%**	**%**	**%**			**%**
Exac. Crohn's	8.0%	7.9%	5.1%	3.9%	3.9%	10.2%	7.1%	6.6%	1%	2%	2%	2%			
Pancreatitis			0	0	1.3%		1.0%								
Abn LFT*			1.3%	1.3%	2.0%							1%			
Abdo pain	0	1%	0	1.3%	2.0%			2.0%**							
Fever	1%	2%			0.7%										
Nausea/Vomit	0	1%	0	0	2.0%		1.0%	2.0%							

	Confirmatory studies					Exploratory studies									
	BUC-23		BUC-52/CDA			BUC-15/CDA			BUC-16/CDA				Gross et al 1996		Caesar et al 1997
	BUC 3mg tid	Pred	BUC 3mg tid	9mg od	Mes 500mg tid	BUC 2mg tid	3mg tid	6mg tid	Placebo	BUC 1mg tid	3mg tid	6mg tid	BUC 3 mg tid	6-MethylPred	BUC 3mg tid →2 mg tid
Asthenia	0	2%													
UTI			0	1.3 %	0										
Depression								2%							

* includes the terms ‘increased hepatic enzymes’, ‘abnormal liver function’ and ‘elevation of liver test’, ‘jaundice’ ** includes a case of epigastric pain

^ excludes exacerbations of Crohn’s disease

Pivotal studies

In both confirmatory studies approximately 5% patients discontinued due to adverse events other than those considered to be associated with exacerbations or complications of Crohn's disease. In Study BUC-23, 4/100 (4.0%) patients in the BUC group and 6/101 (5.9%) patients in the prednisone group discontinued treatment because of AEs. Fever and weakness/asthenia were listed as AEs leading to discontinuation of 2 patients each in the prednisone group. Other AEs leading to discontunuation in that group (1 patient each) were myalgia, muscle cramps, abdominal pain, vomiting, nausea, ileus and elevated creatinine phosphokinase. In the BUC group reasons for discontiuing (all 1 patient each) were fever, myalgia, rash, exacerbation of acne and aphthous stomatitis.

In Study BUC-52/CDA, 1 patient in the BUC 3 mg tid group, 3 in the BUC 9 mg od group and 15 in the mesalazine group discontinued because of AEs. Disconinuations in the BUC group were increased hepatic enzymes (n=1, 3 mg tid group); abnormal liver function, urinary infection and abdominal pain and diarrhoea (all n=1, BUC 9 mg od group). These events were of mild to moderate intensity. Thee of the 4 patients recovered after discontinuaiton from the study and the outcome was unknown in the other. In the mesalazine group, 2 patients discontinued because of pancreatitis and a third patient discontinued with jaundice, abdominal pain and elevated LFTs (NOS). Other reasons for withdrawal included abnormal liver function (n=2) and abdominal pain, fistula discharge, gastroenteritis, allergic dermatitis, headache/nausea/vomiting, fever, hearing loss, diarrhoea and vomiting associated with raised INR, activated partial thromboplastin time (APTT) and Prothrombin Time (PT) (all n=1). All but one patient with diarrhoea recovered in withdrawal from the study. A further 2 patients in the mesalazine group required a dose reduction because of an AE; one because of high temperature (of mild intensity) and one because of nausea, vomiting and epigastric pain (of moderate intensity). Both patients recovered from the AEs and completed the study.

Other studies

An adverse event (other than due to Crohn's disease) was the primary reason for withdrawal of 9 patients in Study BUC-15/CDA; none in the BUC 6 mg group; 4 (4.0%) in the BUC 9 mg group and 5 (4.7%) in the BUC 18 mg group. Reasons for discontinuation in the 9 mg group (all n=1) were impotency, pancreatitis, indigestion and nausea. In the 18 mg group the AEs resulting in discontinuation were (all n=1) depression; gastric pain; nausea and abdominal pain; vomiting and nausea; central venous thombosis left eye; and Cushing's syndrome. All but the case of central venous thombosis were considered to be causally related to the drug.

In Study BUC-16/CDA most discontinautions due to AEs were associated with exacerbations of the underlying disease. Other AEs leading to discontinuation were status asthmaticus (n = 1, placebo); allergic reaction (n = 1, BUC 3 mg), erosive gastritis (n = 1, BUC 9 mg) and perforated gastric ulcer (n = 1, BUC 18mg) and bilirubinaemia (n=1, BUC 18mg).

Gross et al 1996 reported that one patient in the BUC group discontinued due to side effects comprising weight gain, hypotension and psychological disturbance. In the study reported by Caesar et al, 1 patient discontinued due to headache and another with upper abdominal pain.

Evaluator's comment

Table 58 shows the main reason for premature discontinuation of treatment was exacerbation or complications of Crohn's disease. For the recommended 3 mg tid dosage regimen, discontinautions because of other AEs were due to pancreatitis, abnormal LFTs (increased hepatic enzymes (not otherwise specified [NOS])), fever, nausea/vomiting, myalgia, rash, worsening of acne, impotency, indigestion, aphthous stomatitis and anaemia

(all n=1). Reasons for withdrawal in patients receiving 9 mg od doses were abdominal pain/diarrhoea, urinary tract infection and abnormal liver function (NOS), all n=1. Of note, in Study BUC-23, non disease related discontinautions were slightly less in the BUC group than in the prednisone group. In Study BUC-52/CDA the overall discontinaution rates in the BUC groups were approximately 50% of the mesalazine rate, with a slightly higher rate with 9 mg od than 3 mg tid (as was also the case for any AE and any ADR). When withdrawals due to Crohn's disease were discounted, the difference between the budesonide and mesalazine groups in terms of discontinautions due to treatment related AEs was even more marked.

Collagenous colitis

Pivotal study

There was a single withdrawal due to an AE in Study BUC-23. This is discussed under serious AEs.

Other study

One patient in the BUC group withdrew from the study because of an unspecified cardiovascular disorder, fatigue, feeling abnormal and migraine. One patient receiving placebo was noted to have stopped study medication sometime between visits 1 and 2 because of nausea, abdominal pain and hyperhidrosis. However, this patient appeared to have continued the study despite withdrawal of the study medication, with visits 2, 5 and 6 being documented as having been performed but the dates were missing.

Laboratory tests

Liver function in Adult Crohn's

Pivotal studies

There were no clinically significant changes observed in mean LFT values in either of the pivotal confirmatory studies. In Sstudy BUC-23, elevations of AST above the normal range were observed in 4% of BUC patients and 5% of prednisone patients. Similar proportion of patients developed elevated ALT levels in the BUC group but 15% patients developed elevated ALT in the prednisone group. Mean γGT increased with both BUC and prednisone (with a greater increase observed with prednisone; 40% versus 20%). However, only one patient in each group developed levels above the normal range during treatment. Hyperbilirubinaemia developed during treatment in approximately 5% patients in each group.

In Study BUC-52/CDA a higher proportion of patients receiving BUC 9 mg od than patients given BUC 3 mg tid group developed an increased in ALT to above the normal range (8% versus 3% versus 6% for the mesalazine group). Increases in AST to above the normal range were observed in 1% patients in each BUC group compared to 6% in mesalazine group, whilst increases in γGT were observed in 4% patients in all groups. Some 3% patients in the BUC 9 mg od group developed hyperbilirubinaemia compared to 1% of patients in the mesalazine group (no patients in the BUC 3 mg tid group developed hyperbilirubinaemia).

Other studies

In the budesonide dose ranging Study BUC-15/CDA, dose dependent rises in ALT and γGT were observed. Mean percentage changes from baseline in ALT were 2.4 ± 80.0 for BUC 2 mg tid, 9.7 ± 98.7 for BUC 3 mg tid and 17.8 ± 76.8 for BUC 6 mg tid (p=0.0025 for 6 mg versus 18 mg daily, p=0.0162 for 9 mg versus l8 mg daily). This was mirrored by a dose dependent increase in the proportion of patients with increases in ALT above the normal range during treatment; 5.9% versus 8.3% versus 11.1% for the 6mg, 9 mg and 18 mg daily dose, respectively. The mean percentage changes from baseline in γGT were 0.5 ±

39.0 for BUC 2 mg tid, 0.1 ± 72.0 for BUC 3 mg tid and 13.9 ± 53.7 for BUC 6 mg tid (p=0.0006 9 mg versus l8 mg daily), with the proportions of patients with elevated levels being 5.9%, 5.2% and 10.0%, respectively. However, changes in alkaline phosphatase were greatest for the 6 mg daily dose group (2.8 ± 22.4) and similar for the 9 mg and 18 mg daily dose groups (approx 1.0 ± 25%).

In Study BUC-16/CDA, only "clinically noteworthy" abnormalities were presented. One patient receiving BUC 9 mg daily developed elevated AST (0.63, NR 0.1-0.45 mmol/hL) and ALT (1.17, NR 0.1-0.68 mmol/hL) at Day 28. The AST level had returned to normal by Day 42 whereas the ALT level was improved but remained just above the normal range (NR) at that time. The latter had returned to normal by Day 56.

Collagenous colitis

Pivotal studies

Study BUC-35: no monitoring performed

Other studies

Study BUC-44/LMC: no monitoring performed

Kidney function in Adult Crohn's

Pivotal studies

There were no clinically relevant changes in mean creatinine, urea, sodium or potassium levels in either of the confirmatory studies. In Study BUC-23, 11% BUC patients and 8.9% prednisone patients developed at least one potassium sample below the normal range during treatment, whilst in Study BUC-52/CDA, hypokalaemia was observed in 3% of the BUC 9 mg od group, none of the BUC 3 mg tid group and 1% of patients in the mesalazine group.

Other studies

Renal function and electrolytes were not monitored in Study BUC-15/CDA. No "clinically noteworthy" abnormalities were found in any patients receiving BUC in Study BUC-16/CDA.

Collagenous colitis

Pivotal studies

Study BUC-35: no monitoring performed

Other studies

Study BUC-44/LMC: no monitoring performed

Other clinical chemistry Adult Crohn's

Pivotal studies

Blood glucose levels were monitored in Study BUC-23. Mean glucose levels rose in the prednisone (PRED)group from 89.9 ± 31.8 mg/dL at baseline to 93.9 ± 41.6 mg/dL at LOCF, whereas the level was virtually unchanged (in fact a very slight decrease) in the BUC group. This was mirrored by more patients with elevated glucose levels in the prednisone group at each visit and more patients with at least one elevated glucose level during treatment in the PRED group (25% versus 14%), suggesting Budenofalk may offer an advantage in this regard during short term treatment.

Lipase and amylase levels were monitored in Sstudy BUC-52/CDA. Mean serum lipase remained stable in the BUC 3 mg tid group, increased slightly in the BUC 9 mg od group (from 33.74 ± 12.55 U/L to 35.75 ± 16.01 U/L) and increased to a greater extent in the mesalazine group (from 37.31 ± 16.31U/L to 41.93 ± 33.71 U/L). Alpha amylase levels fell

slightly in both BUC groups but increased (from 62.20 ± 23.05 to 64.31 ± 25.57) in the mesalazine group. Correspondingly, increases in lipase levels to above the normal range were not observed in patients in the BUC 3 mg tid group compared with 7% of patients in the BUC 9 mg od and 6% patients in the mesalazine group. No patients in either BUC group developed elevated amylase levels, which can be compared to 4% of mesalazine patients. Two patients in the mesalazine group developed pancreatitis on study.

Other studies

In Study BUC-15/CDA, there were very modest changes in fasting glucose levels with 6 mg and 18 mg daily doses of Budenofalk (mean percentage changes of 0.5 ± 22.3 and 0.0 ± 23.6, respectively) and a 3.5 ± 25.1% mean change with a 9 mg daily dose. However, the proportion of patients who developed elevated fasting blood glucose levels on study was suggestive of a dose response relationship, with 4.4%, 6.7% and 7.5% of patients, respectively for the 6mg, 9 mg and 18 mg daily doses.

One patient who received BUC 3 mg daily was recorded as having a "clinically noteworthy" increase in fasting glucose levels (6.6-6.7, NR 4.2 – 6.1) at Days 42, 56 and 70, which was considered to be causally related to the medication.

Collagenous colitis

Pivotal studies

Study BUC-35: no monitoring performed

Other studies

Study BUC-44/LMC: no monitoring performed

Haematology Adult Crohn's

Pivotal studies

There were no clinically significant changes in mean haemoglobin levels, haematocrit or platelet counts in either confirmatory study. As could be expected with corticosteroids, the mean WCC increased in those groups in each of the studies. In Study BUC-23 this increase was apparent with BUC and prednisone by Week 2, with a much greater change from baseline in the prednisone group (increase from 8.72 ± 3.02 to 12.87 ± 3.62) than the BUC group (increase from 8.31 ± 2.23 to 9.46 ± 3.10). Thereafter, levels slowly decreased in both groups such that by the last study observation the overall change from baseline was greater in the prednisone group (8.72 ± 3.02 to 9.75 ± 3.29) compared to the BUC group (8.31 ± 2.23 to 8.77 ± 2.51). Only one patient from each group had elevated WCC at baseline, whereas during the study 74% of patients in the prednisone group had at least one elevated level during treatment, compared to 34% in the BUC group. In Study BUC-52/CDA, the mean white cell counts increased from baseline to the final visit (LOCF) in both BUC treatment groups, with a greater increase in the 9 mg od group than in the 3 mg tid group (12.8% versus 5.8%). In contrast, the WCC fell slightly in the mesalazine group. Not surprisingly, of all the laboratory parameters monitored during that study, WCC deteriorated most frequently, with increases in counts above the normal range occurring in 17% patients in the BUC 3 mg tid group, 28% in the BUC 9 mg od group and 13% in the mesalazine group.

Other studies

No clinically significant changes in haematology parameters were observed in any of other efficacy studies. However, it was noted that the mean WCC for all groups in Study BUC-15/CDA actually fell from enrolment to the last observation. In Study BUC-16/CDA, 2 patients in the BUC 3 mg daily group, none from the 9 mg daily group and 2 from the 18 mg daily group were considered to have "clinically noteworthy" elevations in WCC.

Collagenous colitis

Pivotal studies

Study BUC-35: no monitoring performed

Other studies

Study BUC-44/LMC: no monitoring performed

Serum cortisol

See PD section of this CER.

Serum osteocalcin

See PD section of this CER.

Electrocardiograph (ECG)

ECG was not performed in any of the efficacy studies.

Vital signs Adult Crohn's

Pivotal studies

Mean values of body weight, pulse and blood pressure remained almost constant thoughout the study in the treatment groups in both of the pivotal confirmatory studies.

Other studies

No clinically significant effects on blood pressure, pulse or weight were found in the BUC groups in Study BUC-16/CDA.

Collagenous colitis

Pivotal study

No clinically significant changes in body weight, pulse or blood pressure was documented for any patients receiving BUC in Study BUC-35.

Other studies

Vital signs were only assessed at screening in Study BUC- 44/LMC.

Clinical safety in adolescents

Studies Providing Evaluable Safety Data

The following studies provided evaluable safety data:

Pivotal efficacy studies

The following safety data were collected in Study BUC-47/CDA:

- General adverse events (AEs) were either reported spontaneously by the patient (at the time it occurred), observed by the study investigator or elicited by a non directive question. The date and time of onset, description, intensity, duration and outcome, aetiology, relationship of the adverse event to study drug and action taken were recorded in the CRF. This was assessed at each study visit (Days 14, 28, 49, 70 and 77). AEs were categorised as serious and non serious using the standard ICH definition. The causal relationship between an AE and study medication was classified according to standard WHO criteria.

- Laboratory tests, comprising standard haematology and biochemistry parameters and urinalysis, were performed at baseline and Days 28 and 70. Summary statistics were calculated for each parameter and the changes from baseline to Day 70 (LOCF) were presented. The number of patients with low or high abnormal laboratory values were summarised for each parameter by treatment group. Contrary to the study protocol, changes in laboratory parameters were not assessed according to total dose or dose/kg.
- Laboratory tests of particular interest were serum cortisol levels and its response to ACTH stimulation, measured at baseline and on Day 49. Absolute serum cortisol levels, changes from baseline and the proportion of patients with normal response to ACTH stimulation were reported.
- Vital signs (blood pressure, pulse, body weight and height) were tabulated at baseline and on Days 28 and 70. Height was also to be assessed at 6 months (Day 182) as part of longer term follow-up on effects on linear growth.
- A global assessment of tolerability by the patient and study investigator at the final/withdrawal examination.

Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome.

Non pivotal efficacy studies

The non pivotal efficacy studies provided safety data, as follows:

- In the open, prospective study reported by Levine et al 2003[55], patients and physicians reported adverse events at each visit at Weeks 2, 4, 8, and 12. Common steroid ADRs such as moon face, acne and hirsutism were recorded and graded separately at each visit by the physician using a 3 point scale (0 points if absent, 1 point if mild and 2 points if prominent or disfiguring). The highest score at any point during treatment was used for side effect quantitative analysis. These side effects were considered medication related only if they were absent at baseline during peak disease activity, and either appeared or became more severe during treatment. Laboratory tests included a blood count, erythocyte sedimentation rate, serum glucose, albumin, transaminase, creatinine, iron and zinc levels. A rapid ACTH test (0.25 mg synthetic ACTH) was performed at baseline and after 12 weeks in all the patients. Adrenal suppression was defined as baseline and 1 h serum cortisol levels <18 µg/dL during an ACTH stimulation test. Vital signs were also assessed at each visit.
- In the retrospective case analysis undertaken by Levine et al 2002[56], side effects were noted from chart review and interviews with gastroenterologists. Of note, there was no attempt to systematically review side effects such as moon face, acne, hirsutism associated with prednisone use because these were considered to be well known and often not reported in charts. A particular focus was the height of the patients, which was converted into gender appropriate height percentiles. No laboratory data were reported.

Other studies evaluable for safety only

Nil studies.

Clinical pharmacology studies

In Study BUC-48/BIO, adverse events were monitored during hospitalisation on Ddays 1 and 8 and elucidated for Days 2 to 7 by the use of non leading questions on the second hospitalisation day. Standard haematology and biochemistry parameters and vital signs were assessed at screening and on Day 9, 24 h after the last dose of Budenofalk. Plasma cortisol levels and urinary excretion of cortisol were measured over 24 h on Days 1 and 8.

Pivotal Studies That Assessed Safety As A Primary Outcome

Nil studies submitted.

Patient exposure

A total of 163 paediatric patients were exposed to Budenofalk oral capsules in the studies submitted, with 12 participating in the clinical pharmacology program, 70 in a Phase IIb company-sponsored dose ranging study (BUC-47/CDA) and 81 in studies of Budenofalk reported in the published literature (Table 59). Of note, however, these studies included patients outside the proposed age range of 12 to 17 years. Of the 12 patients participating in the PK/PD Study BUC-48/BIO, 9 were above the age of 12. In the pivotal Study BUC-47/CDA, of the 70 patients treated only 53 patients (25 in Group 1 and 28 in Group 2) were in the proposed age range. Similarly, the studies by Levine et al 2002[56] and 2003[55] included patients in the age ranges 8 to 18 and 7 to 18 yrs, respectively but it was not possible to discern how many patients in these studies were in the age group proposed for this application. At best, safety data were generated in only 143 patients in the proposed adolescent age group.

The proposed dose of Budenofalk is initial daily dose of 12 mg budesonide in divided doses for 4 weeks, reducing to 9 mg per day (1 capsule each in the morning, at midday and in the evening) thereafter for a total duration of treatment of 8 weeks. All patients in the pivotal Study BUC-47/CDA received treatment for 10 weeks. Patients in Group 2 (n=35/ n=28 adolescents) received the proposed treatment regimen though to Week 8, followed by a further 2 week's treatment with 6 mg (3 mg bd) daily. Patients in Group 1 of the study (n=35/n=25 adolescents) received a dose of 9 mg daily for 8 weeks, followed by a further 2 weeks of treatment with 6 mg daily. In the prospective study undertaken by Levine at al 2003[55], 19 patients received 9 mg daily for 12 weeks. Dosage data were scant in Levine et al 2002[56]; all that was reported was that patients were required to have received a dose of 0.45 mg/kg/day up to a maximum of 9 mg/day for a minimum of 2 weeks.

Table 59. Exposure to Budenofalk oral capsule and comparators in clinical studies in paediatric patients.

Study type/Indication	Controlled studies			Uncontrolled and dose-ranging studies	Total BUC
	BUC	Placebo	Prednisone	BUC	
Clinical pharmacology					
Total				12	12
Children (<12 yrs)				*3*	*3*
Adolescents (12 - 16 yrs)				*9*	*9*
Crohn's disease					
Pivotal (BUC-47/CDA)				70	70
Adolescents (12 -17yrs)				*53*	*53*
< 12 yr or > 17yrs				*17*	*17*

Study type/Indication	Controlled studies			Uncontrolled and dose-ranging studies	Total BUC
	BUC	Placebo	Prednisone	BUC	
Other (lit reports)	81		78		81
TOTAL	81		78	82	163

Adverse events

All adverse events (irrespective of relationship to study treatment)

Pivotal study

Treatment emergent AEs were recorded for 31/35 (88.6%) patients in Group 1 and 34/35 (97.1%) patients in Group 2. The most frequently affected SOCs were the Gastrointestinal system, Nervous system, General disorders and administration site conditions and the Endocrine system, with higher rates being consistently reported for Group 2 (which was closest to the recommended dosage regimen). The most discrepant results between the 2 groups were in the reporting of Respiratory/Thoracic/Mediastinal disorders (2.9% versus 28.6%) which largely due to 6 reports of pharygolaryngeal pain in Group 2 versus nil in Group 1.

The most commonly reported AEs in both groups were headache (Group 1: 28.6% versus Group 2: 42.9%), adrenal suppression (25.7% versus 20.0%), pyrexia (17.1% versus 20.0%), abdominal pain (22.9% versus 14.3%) and worsening of Crohn's disease (22.9% versus 11.4%). Most treatment emergent AEs were of mild to moderate intensity. Severe AEs were observed in 34.3% patients in Group 1 and 22.9% in Group 2 and most of these were due to exacerbations of Crohn's disease.

Other studies

Only ADR data were presented by Levine et al 2002[56] and Levine et al 2003[55] which reported a much lower incidence of AEs in patients receiving BUC (31.6%) than prednisone (71.4%) and particularly side effects such as (acne, moon face and hirsutism). Events considered unrelated to treatment included headache (BUC 1; prednisone 5), pyrexia (BUC 5; prednisone 1) and insomnia (prednisone 1).

In Study BUC 48/BIO, the SOCs most frequently affected by AEs were "General disorders and administration site conditions" (5 AEs in 4/12 patients (33.3 %)), and "Infections and infestations" and "Nervous system disorders" (each with 2 AEs in 2/12 patients (16.7 %)). The most commonly reported events were pyrexia and headache; each reported in 2/12 patients (16.7%). In the majority of patients the AEs were of mild intensity.

Treatment-related adverse events (adverse drug reactions)

Pivotal studies

A total of 19 (54.3%) patients in Group 1 and 23 (65.7%) patients in Group 2 experienced at least one ADR in Study BUC-47/CDA. The most commonly reported ADRs in both dosage groups were adrenal suppression (Group 1 25.7% versus Group 2 17.1%) and headache (8.6% versus 17.1%). Other ADRs reported in 5% or more patients in either group were acne, dyspepsia, nausea, Cushingoid features, arthalgia, dizziness, flushing, pyrexia and hirsutism. The vast majority of ADRs were resolved by the time of last study observation.

Other studies

Levine et al 2002[56] reported that 5 patients in the BUC group and 8 in prednisone group had side effects considered to be related to the medication. Side effects in the BUC group were hirsutism (n=1), moon face (n=2), acne (n=1) and benign intracranial hypertension (BIH, n=1). The case of BIH resolved when treatment was ceased. In the prednisone group ADRs included herpetic infection (n=2), proximal myopathy (n=1) and depression (n=5). Cosmetic effects were not assessed in the prednisone group. A similar range of ADRs were reported by Levine et al 2003[55], with higher rates of individual ADRs reported with prednisone than BUC: muscle ADRs (myalgia, proximal muscle weakness) 35.7% versus 7.7%, p=0.07; moon face 71.4% versus 31.6%, p<0.05; acne 28.6% versus 15.8%; and hirsutism 28.6% versus 15.0%. Adrenal suppression (defined as baseline and 1 h serum cortisol levels < 18 μg/dL during an ACTH test) was present in a single patient who had received prednisone.

In Study BUC-48/BIO, ADRs assessed as being possibly causally related to BUC were recorded for 4/12 (33.3 %) patients. These were asthenia, muscle twitching of the eye lid and a perianal abscess observed in one patient and reports of irritability, skin rash and intermittent tiredness in separate patients.

Evaluator's comment

Studies using Entocort have not been formally evaluated in this CER. Escher et al 2004[57], in a direct comparison of Entocort (9 mg daily for 8 weeks then 6 mg daily for 4 weeks) and prednisolone (1 mg/kg/day for 4 weeks then tapering to 2.5 mg/day over 8 weeks) found 11/22 (50%) paediatric patients receiving Entocort and 20/26 (77%) patients receiving prednisolone experienced at least one glucocorticosteroid side effect (such as moon face buffalo hump, acne, hirsutism, striae, bruising, swollen ankles, hair loss, mood swings, depression and insomnia), p=0.03. Moon facies was almost thee times as common in the prednisolone group (p=0.01) and acne was also reported significantly more often (p=0.033).

Escher et al[57] also found that the frequency of moon face in children during prednisolone treatment (in 15/26, 58%) is almost twice that reported in adults receiving prednisolone 40 mg daily in other studies (25%-35%). For budesonide, the difference was similar but less striking: 5/22 (23%) children developed moon face during treatment compared to 7%-17% of the adults. Striae were not reported in adults, while the incidence was 12% in paediatric patients. Of note in Escher's study was that all children in the Entocort group received 9 mg (and then 6mg) daily, irrespective of age or weight, suggesting the apparent higher incidence of steroid related effects may be due to a higher dose per kg in children compared to adults. However, they reported that they had not been able to demonstrate any correlation between budesonide dose per kg and side effect frequency (data not actually provided in the publication).

Deaths and other serious adverse events

Pivotal study

There were no deaths recorded in any of the paediatric studies. Treatment emergent SAEs occurred in 10/35 (28.5%) of patients in Group 1 and 6/35 (17.1%) of patients in Group 2. In all cases, the reason for classifying the AE as serious was hospitalisation and the causality was as unlikely related to the study medication. All but 3 SAEs in Group 1 (localised foot infection; inguinal hernia; and gastroenteritis) and 1 in Group 2 (accident/facial injury) were consistent with exacerbations of Crohn's disease.

Other studies

There were no SAEs in the clinical pharmacology Study BUC-48/BIO. The two papers by Levine et al did not mention serious AEs.

Discontinuation due to adverse events

Pivotal study

In Study BUC-47/CDA, 11 (31.4%) patients in Group 1 and 6 (17.1%) patients in Group 2 withdrew from the because of an AE. The most common reason for withdrawal was exacerbation of Crohn's disease (6 patients in Group 1 and 4 patients in Group 2). Other AEs leading to early termination were abdominal pain NOS (2 per group), rash (1 per group), localised foot infection (n=1, Group 1).

Other studies

There were no withdrawals due to AEs in the clinical pharmacology study. No information was provided in the papers by Levine et al. 2002[56] and 2003[55].

Laboratory tests

With the exception of vital signs, the results below are presented for the pivotal Study BUC-47/CDA only. The papers authored by Levine et al 2002[56] and 2003[55] did not contain any laboratory parameter data. In the clinical pharmacology Study BUC-48/BIO, there were no clinically significant changes in laboratory parameters (including LFTs, amylase, lipase and differential WCC) identified during the study.

Liver function

Statistically significant changes from baseline to final visit (LOCF) as indicated by 95%CIs were:

- alkaline phosphatase activity decreased in Group 2 (-14.62 U/L [95%CI: -28.06 to -1.18]), whereas no relevant change was observed in Group 1 (-3.39 U/L [95%CI: -12.42 to 5.64]); and
- albumin concentrations increased in Group 1 (0.227 g/dL [95%CI: 0.057 to 0.396]), whereas in Group 2 (0.163 g/dL [95%CI: -0.077 to 0.403]) only a tendency to increased levels was observed.

These changes are not clinically significant, although the changes in albumin concentration would be consistent with improvement of Crohn's disease.

None of the patients in either group developed abnormally high AST, bilirubin or LDH levels during treatment. Elevations of ALT were found in 8% patients in Group 2 (none in Group 1); γGT in 9% patients in group 1 (none in Group 2) and alkaline phosphatase in 4% in group 1 (none in Group 2).

Kidney function

No statistically or clinically significant changes from baseline to last visit (LOCF) were found in creatinine of electrolyte concentrations. No patients in either group developed elevated creatinine or urea levels and only one patient (from Group 1) developed hypokalaemia during treatment. Abnormally high sodium levels were observed in 5% patients in Group 1 and 7% patients in Group 2.

Other clinical chemistry

There were no statistically or clinically significant changes from baseline to last visit (LOCF) in blood glucose levels. Only one patient (from Group 1) developed an abnormally high glucose level during treatment.

Haematology

Statistically significant changes from baseline to final visit (LOCF) as indicated by 95%CIs were observed in:

- the proportion of eosinophils in the WCC differential, which decreased in both treatment groups (Group 1 -0.9047% [95%CI: -1.4719 to -0.3375] Group 2: -0.7694% [95%CI: -1.3345 to -0.2042]);
- the proportion of lymphocytes in the WCC differential increased in Group 2 (2.8375% [95%CI: 0.4882 to 5.1868]) whereas there was no change was observed in Group 1 (0.2594% [95%CI: -2.6935 to 3.2124]); and
- the number of platelets decreased in both treatment groups (Group 1: -64.0 x 10^9/L [95%CI: -97.7 to -30.4], Group 2: -47.7 x 10^9/L [95%CI: -78.1 to -17.2]).

These changes in laboratory parameters were thought to indicate the anti-inflammatory effect of budesonide (such as a decrease in eosinophils) and the improvement of Crohn's disease under budesonide treatment (such as a decrease in platelets). Also, although not statistically significant, the WCC showed a tendency to a decrease in Group 2 (-0.642 x 10^9/L [(95%CI: -1.290 to 0.005]), whereas no relevant change was observed in Group 1 (0.381 x 10^9/L [95%CI: -0.711 to 1.473]).

Serum cortisol

See PD section of this CER.

Electrocardiograph

Not assessed in any study.

Linear growth

Pivotal study

In Study BUC-47/CDA the average height percentile was clearly lower for both BUC groups at the 6 month follow up assessment when all patients with a value at baseline and all patients with a value at 6 months were compared. In Group 1, the mean (± SD) percentile at baseline was 34.6 ± 27.9 (n=34), whereas at the 6 month follow-up it was 26.3 ± 32.1 (n=15). In Group 2 the mean percentile had fallen from 38.8 ± 29.8 (n=35) to 29.4 ± 25.5 (n=19). However, a considerable proportion of patients did not have follow-up assessment and when data from only those patients with a value at both times were used no difference in height percentile could be observed. For these patients, in Group 1 (n=14) the mean percentile changed from 29.6 ± 33.5 to 28.0 ± 32.6. In Group 2 (n=19) the mean percentile changed from 28.0 ± 27.5 to 29.4 ± 25.5.

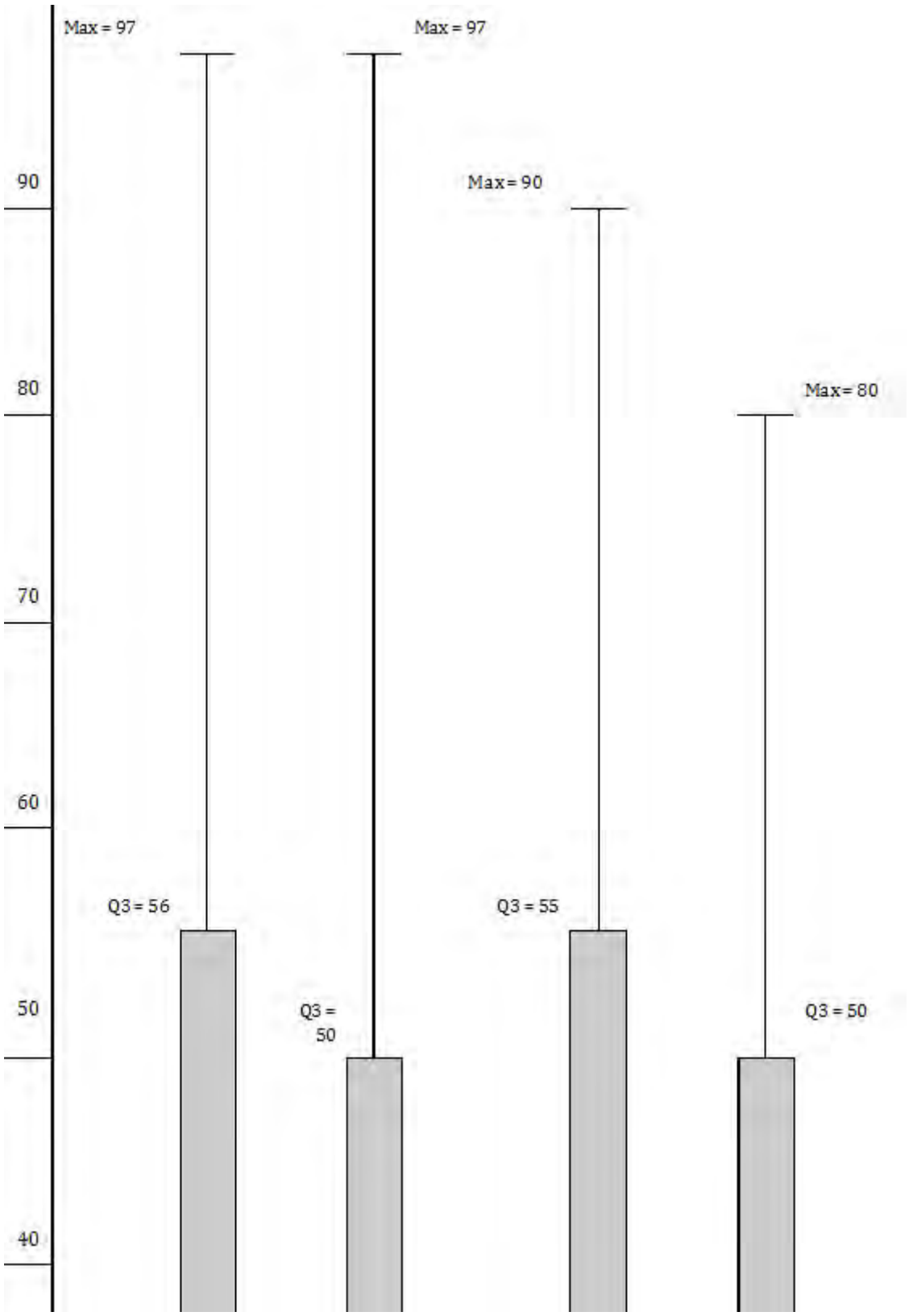
Other studies

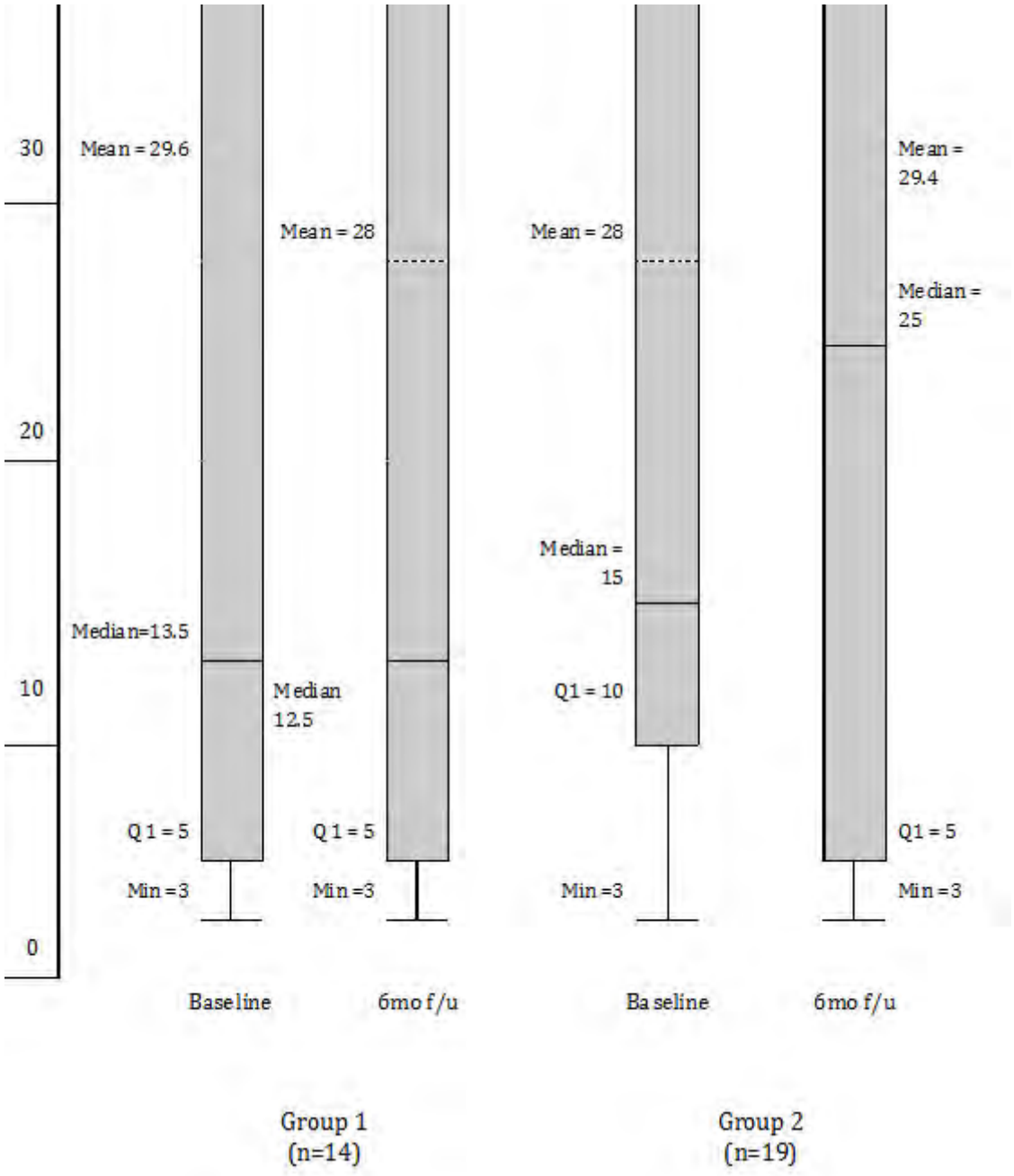
In the study reported by Levine et al 2002[56], data on post remission linear growth was available for 20 budesonide responders and 21 prednisone responders. The mean change in height percentiles during 6 months for patients who achieved remission in the BUC group was +0.25 ± 4.5 centiles compared with -2.35 ± 5.4 centiles for the prednisone group, p=0.1. In the same study, mean weight gain at 8 weeks was significantly higher in prednisone responders (4.6 ± 4.17 kg) than BUC responders (2.54 ± 2.7 kg).

Evaluator's comment

In Study BUC-47/CDA, even though the changes in mean height percentile for patients with a full data set were unchanged, it is useful to consider the spread of data (median score and interquartile range) to have a better understanding of how linear growth may have been impacted. Box and whisker plots of summary statistics at the two time points for the two groups are shown in the Figure 25. These are graphical summaries of the range, interquartile range (denoted by the box), the median (solid line within the box) and the mean (broken line in the box). Thus, half the data falls within the box and the other half is contained in the whiskers (a quarter per whisker).

Figure 25. Box and whisker plots of height percentiles in paediatric Crohn's disease patients before and after treatment with Budenofalk – study BUC-47/CDA. Figure continued across two pages.





What is apparent from these plots is:

- all the distributions were right skewed (median score less than mean), in which case a comparison of geometric means would have been preferable to arithmetic means;
- 75% of patients in each group were below 56th percentile for height at baseline which is probably a reflection of the impact of the underlying disease and previous treatments;

six months post treatment 75% of patients in each group were now below the 50th percentile. Also, despite the increase in mean and median percentile scores in Group 2, a greater impact appears to have occurred in this group in that the maximum percentile had fallen from the 90th to the 80th (which means that at least one patient crossed from the 90th to the 80th percentile) and the lower quartile reduced from 10th to the 5th percentile, such that 25% patient now lay below the 5th percentile whereas they previously fell below the 10th percentile.

However, no firm conclusions can be drawn from either Study BUC-47/CDA or Levine et al 2002[56] because the number of patients receiving Budenofalk was very small and there was no adjustment the possible impacts of post remission maintenance therapy, disease activity or nutritional support.

Kundhal et al 2001[58], as part of a retrospective study, examined the impact of maintenance therapy with Entocort on the linear growth of 6 Tanner Stage I patients with Crohn's disease involving the ileum with or without proximal colon involvement (age range 11.4 to 13.4 years, with 5/6 older than 12 years). In comparison with pre treatment growth rates, during maintenance therapy with Entocort height velocity either remained poor or became abnormally slow for age, despite weight gain and a paucity of gastrointestinal or extraintestinal symptoms. The mean rate of growth observed during the 6 month period after initiation of Entocort treatment was 2.3 ± 1.0 cm/year compared with 3.0 ± 1.8 cm/year during the 6 months before treatment (p=0.31). Furthermore, Entocort was stopped in all but two patients after 6 months (because of poor linear growth). Although the maintenance of remission is not sought as an indication, the findings of Kundhal et al[58] may have implications for children receiving repeated courses of Budenofalk for recurrent flares of disease.

Vital signs

There were no clinically significant changes in blood pressure, pulse rate or body temperature during the 10 weeks of treatment (LOCF) in Study BUC-47/CDA. Levine et al 2002[56] and 2003[55] did not report vital signs data.

Postmarketing experience

Post marketing experience were submitted in the form of 2 PSURs dated 2003 (covering the period International birthday to December 31 2002) and 2008 (covering the period 1 January 2003 to 30 April 2008). These provided cumulative distribution and ADR data up to 30 April 2008. In addition, a case line listing of all suspected adverse drug reaction reports for the period 1 May 2008 to 15 November 2009 were provided without analysis or summarisation.

No regulatory actions were taken in that time (from launch to 30 April 2008). The EU Summary of Product Characteristics (SmPC) was updated with safety information in 2003 to include liver cirrhosis with signs of portal hypertension as a contraindication and to clarify labelled interactions with CYP450 3A inhibitors and inducers and to advise that concomitant use of oestrogens or OCP may result in increased plasma levels of corticosteroids.

Relatively few suspected ADRs have been reported post approval for the oral capsules, with 25 suspected ADRs in 19 patients from market introduction to December 31 2002; 23 ADRs in 19 patients from January 2003 to April 30 2008; and 24 ADRs in 17 patients from May 2008 to November 2009, giving a total of 72 ADRs in 55 patients. (Note: the first PSUR included two reports of portal vein thombosis that developed in the PD/PK Study BUC-39/BIO (reported in Hempfling et al 2003[38]) and second PSUR also included several ADRs that were denoted as having occurred in Study BUC-16/CDA. These have not been counted here as they were considered under the premarketing data).

In keeping with the premarket experience, the most commonly affected SOCs were the Gastrointestinal system (15 ADRs, including 2 reports of pancreatitis); Skin and appendages (11 ADRs, including 2 reports of acne, 2 reports of ecchymosis, 1 report of skin thinning and 1 report of toxic epidermal necrolysis that required skin grafting in a 10 year old patient with Churg-Strauss-Syndrome); the Central nervous system (7 ADRs, including only 1 report of headache but 3 reports of pseudotumour cerebri/BIH); Infections and infestations (6 ADRs, including a report of ophthalmic herpes zoster); and Musculoskeletal disorders (6 ADRs, including 2 reports of osteoporosis and 1 report of

necrosis of the femoral head). Other reactions included diabetes mellitus (n=1), Cushing's syndrome (n=2) and adrenal insufficiency (n=1).

The 3 cases of benign intracranial hypertension (BIH; all with papilloedema) occurred in adolescents (ages 13, 14 and 15 yrs; 2 male, 1 female) with Crohn's disease and poor nutritional status who had previously received multiple courses of prednisone for treatment of their disease without developing intracranial hypertension. The BIH resolved when Budenofalk was withdrawn and did not recur with subsequent use of prednisone. These cases were published by Levine et al 2001[93]. This ADR is known to be associated with steroid therapy, particularly on withdrawal of therapy and has been included in the draft PI for the product.

The reasons for use of Budenofalk capsules were quite varied and included Crohn's disease (n=21); ulcerative colitis (n=9); collagenous colitis (n=5); inflammatory bowel disease (IBD) NOS (n=3); autoimmune hepatitis (n=3); lymphocytic colitis (n=2); microscopic colitis (n=1) and eosinophilic enterocolitis (n=1). The reason for use was not given for 6 reports and other conditions accounted for an additional 4 reports. There was no particular pattern of reactions attributable to specific underlying conditions. However, amongst the 'other' conditions was a case of "chonic diarrhoea" for which the patient presented with Cushing's disease and adrenal insufficiency after 4.5 years ongoing treatment with Budenofalk. There was no apparent confirmation of an underlying IBD in this patient and this case highlights the potential for long term use of the product for quite a non-specific symptom.

Many of the ADRs were assessed as being serious but most of these were either due to the underlying disease or were reactions known to be associated with steroid therapy. Unexpected serious ADRs included a case of acute hepatitis (characterised by marked increases in ALT to >1000U/L at day 20) in an human immunodeficiency virus (HIV) positive patient who was treated with Budenofalk oral capsules 9 mg/day for severe pancolitis of the rectum post radiation for rectal carcinoma (published by Sager et al 2002[94]). There was a positive de-challenge and positive rechallenge (in terms of ALT levels) for budesonide. Liver biopsy showed evidence of liver cell necrosis consistent with acute toxic parenchymal damage. Concomitant medications included ritonavir and clarithomycin which are inhibitors of CYP450 3A and it was concluded that there had been an accumulation of budesonide leading to the hepatitis as a result of an interaction with these medications. Plasma budesonide levels were not available.

There were three other previously unreported serious ADRs, all assessed as unlikely to be related to budesonide

Overall, the post marketing experience with Budenofalk was consistent with the safety profile observed in the clinical trials.

Specific safety issues of regulatory importance

Liver and Haematological toxicity/ Serious skin reactions/ Cardiovascular safety/ Unwanted immunological events

Nil new issues identified over and above the known safety profiles of budesonide and glucocorticosteroids more generally.

[93] Levine A. et al (2001). Benign Intracranial hypertension associated with budesonide treatment in children with Chrohn's disease. Abstract. Journal of Child Neurology. 16: 458-461.

[94] Sager A, Wettstein M, Oelie M et al. Budesonide-induced acute hepatitis in an HIV-positive patient with ritonavir as a co-medication. *AIDS* 2002; **16(8)**: 1191-1192.

Other safety issues

Safety in special populations

See above for safety in the adolescent population. Safety in the elderly and patients with hepatic impairment were not presented separately.

Safety related to drug-drug interactions and other interactions

Potential for pharmacokinetic interactions have been discussed above. The details of a case of acute hepatitis attributable to an interaction between Budenofalk, ritonavir and clarithromycin have also been discussed in this CER.

Evaluator's overall conclusions on clinical safety

Budesonide is a non-halogenated glucocorticoid corticosteroid with a safety profile that has been well characterised in relation to its clinical applications in asthma (for example with Pulmicort Turbuhaler) and IBD (such as Entocort). The studies submitted with this application have demonstrated that those side effects typically associated with glucocorticosteroids including adrenal suppression clearly occur with Budenofalk. In the placebo controlled dose ranging Study BUC-l6/CDA, the incidence of steroid-induced AEs (ADRs) was shown to increase with increasing dose and is in keeping with a dose dependent effect of budesonide on plasma cortisol and responses to ACTH stimulation and on osteocalcin levels.

The rationale for the use of budesonide with its high ratio of topical to systemic activity is that it should reduce the potential for corticosteroid-related systemic side effects. Such an advantage has been demonstrated in patients with Crohn's disease. In a direct comparison with prednisone (Study BUC-23), the frequency of the 5 most closely steroid related effects (moon face, acne, buffalo hump, hirsutism and skin striae) was significantly lower with Budenofalk (44% versus 67%; p = 0.0018, two-sided Fisher's exact test). Similarly, Gross et al 1996[40] found a lower rate of ADRs in patients receiving Budenofalk (28.6%; 95% CI 14.6% - 46.3%) than in those receiving 6-methylprednisolone (69.7%; 95% CI 51.3%-84.4%), p=0.0015.

Budenofalk was also better tolerated than mesalazine in the pivotal confirmatory Study BUC-52/CDA where the overall withdrawal rate for Budenofalk was approximately 50% of the mesalazine rate. When withdrawals due to exacerbations Crohn's disease were discounted, the difference between the budesonide and mesalazine groups in terms of withdrawal due to treatment related AEs was even more markedly in favour of Budenofalk.

The safety profile of Budenofalk in children and adolescents appears similar to that in adults, although the numbers of patients exposed was substantially lower. Notwithstanding the lower patient exposure, the advantage of Budenofalk over conventional corticosteroids in terms of steroid induced effects appears to exist for this patient population as well. Levine et al 2002[56] reported that 5/62 (8.1%) patients who received Budenofalk and 8/58 (13.7%) patients receiving prednisone had side effects considered to be related to the medication. Levine et al 2003[55] found higher rates of individual ADRs reported with prednisone than Budenofalk: muscle ADRs (myalgia, proximal muscle weakness) 35.7% versus 7.7%, p=0.07; moon face 71.4% versus 31.6%, p<0.05; acne 28.6% versus 15.8% (p value not reported); and hirsutism 28.6% versus 15.0% (p value not reported).

Issues of particular note with respect to use of Budenofalk in adolescents include:

- benign intracranial hypertension
  - 4 cases have been identified (1 in premarket studies and 3 from post marketing surveillance). All cases were associated with papilloedema and all cases resolved

on withdrawal of Budenofalk. In 3 cases the patient had previously received prednisone without developing intracranial hypertension and the BIH did not recur with subsequent use of prednisone. This ADR is known to be associated with steroid therapy, particularly on withdrawal of therapy and has been included in the draft PI for the product;

- there is a paucity of long term effects of Budenofalk on linear growth and no data on bone demineralisation
  - Although relevant data were available in Study BUC-47/CDA or Levine et al 2002[56], no conclusions can be drawn about the impact of Budenofalk on liner growth because the number of patients receiving Budenofalk was very small and there was no adjustment the possible impacts of post remission maintenance therapy, disease activity or nutritional support. Of note, a study of Entocort in paediatric Crohn's disease (Kundhal et al 2001[58]) found that compared to pre treatment growth rates, height velocity either remained poor or became abnormally slow for age, despite weight gain and good disease control during maintenance therapy with Entocort over 6 months in 6 patients, 5 of whom were aged 12 – 13.5 years. Although the maintenance of remission is not sought as an indication for Budenofalk, these findings may have implications for children receiving repeated courses of Budenofalk for recurrent flares of disease; and
- the incidence of certain corticosteroid steroid ADRs such as moon facies and skin striae is higher in children and adolescents than in adults; however the difference for budesonide (Entocort) appeared to be less than for prednisolone.
  - Limited safety data were available for patients receiving Budenofalk for the treatment of collagenous colitis. No particular pattern of AEs or ADRs appears to be associated with the use of Budenofalk in this specific treatment population. However, it must also be noted that there were no prospective strategies to detect other adverse effects (for example on laboratory parameters) utilised in any of the studies submitted

List of questions

Evaluation of responses to clinical questions

Four questions were proposed by the clinical evaluator after the first round evaluation. However, the sponsor was also sent additional questions relating to the evaluator's comments thoughout the report. The questions and evaluator's evaluation of the sponsor's responses have been reproduced below:

Pharmacokinetic issues

1. Detectable levels of budesonide at baseline in Studies BUC-5.C3 and BUC-5.C9/BUC-5.C18

The sponsor was asked to comment on the cause of detectable levels of budesonide at baseline for a number of subjects in Studies BUC-5.C3 and BUC-5.C9/BUC-5.C18. No definitive explanations could be given. The sponsor noted that during the development program questions were raised about the validity of the RIA and HPLC/RIA methods and this led to a subsequent PK study (BUC-59/BIO) that was conducted using state of the art methods (HPLC/MS/MS). Results from that study were noted to be similar to results from the earlier studies.

2. Clarification of the conduct of studies BUC-5.C3 NBF_BF and BUC-5.C9 NBF_BF

The evaluator sought clarifying information about the conduct of these 2 PK studies, which have been evaluated in this CER. In response to these questions, the sponsor:

- conceded that the older PK and PD studies were not compliant with all aspects of current standards for such studies;
- confirmed that Study BUC-5.C3 NBF_BF was a single way cross over study and not a single-dose, open, randomised cross over design as had been stated in the Study Protocol;
- confirmed that there had indeed been protocol amendments for Studies BUC-5.C3 NBF_BF and BUC-5.C9 NBF_BF, such that PK samples were not required to be taken at 5, 7, 18, 20 and 22 h. However, it is clear that samples were required to be taken at 0.5 and 1.5 h but in a number of instances these were not collected. The sponsor suggested the fact that other trials had shown that there was a lag-phase of about 2-4 h may have influenced the investigators' decision not to collect the samples as required; and
- had no explanation as to why subject 7 did not have any pharmacokinetic profiling of budesonide in the fasted state in Study BUC-5.C9 NBF_BF.

Other issues

General

1 Provision of company reports for Studies BUC-2/CDA, BUC-4/CDA, BUC-18/BIO and BUC-39/BIO

It was noted that the sponsor had submitted published papers for studies that had in fact been the subject of final company study reports. The sponsor had indicated in the original submission that this was done to keep the clinical documentation to a reasonable size. The sponsor was asked to provide the final study reports.

In response, the sponsor indicated they had considered the studies to be of minor relevance and therefore it was appropriate to submit papers to keep the clinical documentation to a reasonable size. The sponsor also provided a brief justification for each study in support of this statement, as follows:

Study BUC-4/CDA was an open label and non controlled pilot study and the second phase of the study used a different dosage regimen to that requested in the submission;

Study BUC-2/CDA was a small controlled pilot study and, given the availability of 4 larger randomised studies, this study was of minor importance;

Study BUC-18/BIO was an investigator-controlled PK study conducted in patients with ulcerative colitis; and

Study BUC-39/BIO was a PK study conducted in patients with primary biliary cirrhosis.

The clinical evaluator agrees that, in the context of the overall clinical development program, the studies are considered to be of minor importance from the point of view of establishing the efficacy and pharmacokinetic profile, respectively, in the target population. In particular, the study reports for BUC-2/CDA and BUC-4/CDA confirmed the fact that these studies were pilot studies that used sample sizes that were based not on any *a priori* power calculations but rather previous experience with recruitment at participating centres. Also, the two PK studies were performed in off-label populations. However, it should be noted that the PK Study BUC-39/BIO was the basis for the clinically important contraindication for patients with late stage hepatic cirrhosis.

The value of the company study reports is that collectively they:

- provided full accountability of participant flow/disposition, with detailed analyses of withdrawals and drop outs;

- confirmed the adequacy of drug accountability and quality assurance measures employed in the studies; and
- provide detailed descriptions of how safety /tolerance, including adverse events and adverse reactions and effects on laboratory parameters had been assessed.

None of these aspects were described adequately in the published papers. As a case in point, one of the clinical evaluator's criticisms of Hempfling et al 2003[38] (the published paper based on Study BUC-39/BIO) was the absence of information about treatment compliance and protocol violations and deviations. The published paper had simply stated that 19 patients had been enrolled. However, it was apparent from the company study report that 23 patients were actually enrolled and that 3 of these patients completed the study twice. During their first enrolment these 3 patients had had a "false intake of study medication" and the corresponding data were appropriately excluded from the PK analysis. On subsequent re-enrolment the patients were assigned new identification (ID) numbers and completed the study for a second time without incident and appropriately the resulting data were included in the PK analysis. The study report also revealed that data were excluded from a further 4 of the 23 patients because of major protocol deviations (leaving a total of 19 patients, as reported by Hempfling et al[38]). Reasons for the exclusion of data from the additional 4 patients were: ingestion of 2 additional tablets on the final day (n=3) and non compliance with medication (n=1). The exclusion of these data was appropriate. In conclusion, although the additional information provided by the company study report did not change the actual PK results or conclusions reported by Hempfling et al[38], it allowed for a more complete understanding of how the study was conducted and for an independent assessment of whether the exclusion of data from analysis had been appropriate.

With regard to the safety data provided by Studies BUC-2/CDA and BUC-4/CDA for the target population, the adverse event profiles observed for budesonide were very similar to those of the pivotal studies. Of importance, detailed analyses of laboratory values showed no systemic changes in any haematological or biochemical parameters in Study BUC-2/CDA, whilst in Study BUC-4/CDA only a statistically and clinically significant/desirable decrease in ESR was observed after all phases of treatment.

2. Company report for Study BUC-9

Study BUC-9 had been cited in the report for Study BUC-14/BIO. The sponsor was asked to provide either the final study report or a justification for not doing so. In response, the sponsor provided both.

It was apparent that the sponsor had not originally submitted the study report because the study was not conducted in the target population. This justification is acceptable and the study has therefore not been considered further by the clinical evaluator.

Evaluator's conclusions on the sponsor's response

The sponsor has addressed all the questions raised.

The responses on the pharmacokinetic issues serve to highlight the fact that the studies were old and not of a contemporary standard and used a questionable assay. This was recognised during the development program by the sponsor who subsequently undertook a PK study using a state-of-the-art assay. The results from that study (BUC-59/BIO) yielded results consistent with those from earlier studies. Consequently, these issues can be considered to be resolved.

Study reports were provided for Studies BUC-2/CDA, BUC-4/CDA, BUC-18/BIO and BUC-39/BIO which were originally submitted as published papers in support of the indication adult Crohn's disease. The full study reports allowed for a much more detailed examination of participant flow/disposition, drug accountability and safety/tolerance,

including how adverse events and adverse reactions and effects on laboratory parameters had been assessed. These aspects of theses studies can now be considered to be acceptable. Importantly, no additional issues have been identified from the full study reports by the clinical evaluator. Consequently, the clinical evaluator's original recommendation regarding approval of the indication is confirmed.

Clinical summary and conclusions

Treatment of Adult Crohn's Disease

Preliminary Assessment of Benefits

The benefits of Budenofalk oral capsules in the proposed usage in adult patients with mild to moderately active Crohn's disease of the ileum and/or colon are:

- induction of remission (CDAI <150) in greater than 50% patients;
- clinically significant reductions in disease activity (as measured in CDAI scores) in patients not achieving remission; and
- these benefits are achieved with fewer side effects than conventional glucocorticosteroids.

Preliminary assessment of risks

The risks of Budenofalk oral capsules in adult Crohn's disease are those side effects typically associated with glucocorticosteroids including adrenal suppression. However, direct comparisons of Budenofalk with prednisone (Study BUC-23) and 6-methylprednisolone (Gross et al 1996[40]) indicate the frequency of steroid related effects (such as moon face, acne, buffalo hump, hirsutism and skin striae) is significantly lower with Budenofalk oral capsules. Budenofalk was also better tolerated than mesalazine in the pivotal confirmatory Study BUC-52/CDA.

Preliminary Assessment of Benefit-Risk Balance

The benefit-risk balance of Budenofalk oral capsules, given the proposed usage, was considered to be favourable.

Preliminary Recommendation Regarding Authorisation

Budenofalk (3 mg budesonide) oral capsules should be approved for the treatment of mild to moderate active Crohn's disease of the ileum and/or colon.

Final benefit-risk assessment and recommendations

Note: This final assessment of risks and benefits and the accompanying recommendations take into account any responses to clinical questions raised at the end of Round one, evaluated above in this report.

Treatment of Adult Crohn's disease

After consideration of the responses to clinical questions, the benefits, risks and benefit-risk balance of Budenofalk oral capsules in the treatment of adult Crohn's disease are unchanged from those above.

Final recommendation regarding authorisation

- Budenofalk (3 mg budesonide) oral capsules should be approved for the treatment of mild to moderate active Crohn's disease of the ileum and/or colon.

V. Pharmacovigilance findings

A Risk Management Plan was not submitted with the current submission.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations, which formed two parts: Foam Enema and Enteric Capsules:

Foam enema

Quality

There were no objections to registration of Budenofalk foam enema in respect of chemistry, manufacturing and controls to registration. The quality evaluator noted that the foam enema is an emulsion in an aluminium canister. The canister is pressurised with the propellants propane, butane and isobutane. Each can is intended to deliver 14 x 2 mg doses and contains a 20 mg overage of budesonide (48 mg in total). Budesonide is intended to act locally. After rectal administration, the systemic availability of budesonide is about 18 – 30%. There was no systemic accumulation of budesonide upon multiple dosing of the foam enema.

Nonclinical

There were no nonclinical objections to registration. The evaluator noted that the clinical systemic exposures (plasma AUC) to budesonide at the maximal doses of Budenofalk foam enemas were less than budesonide exposure from the MRHD of Entocort® capsules (9 mg/day).

Budesonide is highly protein bound in plasma, with approximately 90% of budesonide bound to plasma proteins in humans, rats and dogs.

Clinical

Pharmacology

The evaluator has noted that sorbic acid was used as a preservative in the formulation used in clinical trials for Budenofalk foam enema however it is replaced with propylene glycol in the product proposed for registration.

Two PK studies were performed for the foam enema, a multidose study in 18 healthy volunteers and a single dose ^{99m}Technetium-labelled budesonide study in 12 patients with either left sided colitis spread of budesonide from the foam enema. These studies are discussed in the CER above. Considerable inter-individual and intra-individual variation in PK was seen. On Day 5 of study the ratio of C_{max} for Dose 2: Dose 1 on Day 5 (calculated by the clinical evaluator) ranged from 0.45 to 2.56 (mean ± SD 1.24 ± 0.59; median 1.11; CV 48%). t_{max} also varied between the two doses on Day 5 with the Dose 2: Dose 1 ratio ranging from 0.25 to 5.3 (mean ± SD 0.96 ± 1.24; median 0.5; CV 129%). Overall systemic bioavailability was 13.8% on multiple dosing in healthy volunteers but was not assessed in patients with ulcerative colitis. There was no evidence of accumulation with multiple dosing in healthy volunteers.

In the single dose study radioactivity was noted in the distal half of the sigmoid colon within 0.5 h, peaking at 2 h then remaining stable over 2 to 6 h post administration, accounting for 21.0 to 27.4% of total activity. In the proximal half of the sigmoid colon,

budesonide reached a maximum of 13.9% of radioactivity at 2 h and remained relatively stable until 6 h after administration. The maximum level of radioactivity in the distal third of the descending colon ranged between 0 – 53% with a mean of 12.4% and 8.5% at 4 and 6 h post dose respectively.

Four studies included assessment of the pharmacodynamic effects of systemic exposure to budesonide foam. Assessments were of: the effect on HPA axis; bone metabolism; blood lymphocyte and granulocyte counts; and on C-reactive protein.

No clinically significant decreases in mean morning serum cortisol, serum bone-specific alkaline phosphatise or serum osteocalcin when the foam was administered daily for up to 8 weeks in patients with active ulcerative colitis. No effect on serum aldosterone or serum electrolytes was noted with rectal doses of up to 4 mg daily for 6 weeks.

The effect of budesonide foam on CRP was limited due to the lower baseline levels of CRP in the higher dose (4 mg daily) rectal foam group compared with the 2 mg daily and placebo groups. No large reductions were seen in any group in Study BUF-5/UCA (a dose finding study). The clinical evaluator has noted that after 6 weeks of treatment with 2 mg budesonide enema daily a statistically significant HPA axis suppression compared to placebo has been seen with use of another budesonide enema (Entocort) that is not registered in Australia.

Efficacy

Dose finding was limited with the sponsor relying mostly on published papers using the proposed budesonide dose in other enema formulations. The sponsor conducted one dose finding study (BUF-5/UCA) with Budenofalk foam enema however in this study there was no statistically significant difference between budesonide 2 mg/day or 4 mg/day and placebo for any of the efficacy parameters examined. This was attributed to the higher than expected response rate of 61% in the placebo group in this study.

The studies identified by the sponsor as pivotal are BUF-9/UCA and BUF-6/UCA. Only BUF-9 was double blind. BUF-9 was a randomised, double-blind study in which Budenofalk foam enema (BUF) 2 mg/25 mL with Entocort (budesonide) enema (EBE) 2 mg/100 mL in patients with active ulcerative proctitis or proctosigmoiditis. This study is described the CER. Patients were aged from 18 to 70 years with an established or new diagnosis of proctitis or proctosigmoiditis and a Clinical Activity Index (CAI) of >4 and ≤ 12 and an Endoscopic Index ≥ 4. Patients received either BUF foam and placebo enema or placebo foam and EBE enema for 4 weeks. Because the foam and enema couldn't be given at the same time, one medication was given in the morning and the other in the evening with patients stratified to either morning foam and evening enema or *visa versa*.

The primary efficacy variable was the CAI. The Disease Activity Index, Endoscopic Index, Histological Index and Physician's Global Assessment were secondary efficacy variables. The primary efficacy endpoint was clinical remission, defined as a CAI ≤ 4 at the final/ withdrawal examination. This was a non-inferiority study with the non-inferiority limit of -15% for absolute difference in remission rates. The primary analysis was of the *per protocol* population.

A total of 541 patients were randomised, 537 treated and 482 completed the study, 239 given BUF and 243 given EBE. At baseline, 47.1% of patients were male, over 99% were Caucasian, 76.7% had established disease with 61.7% having proctosigmoiditis. Median duration of UC was 4.0 years (range 0 – 39.8 years) and median duration of the present acute episode was 5.4 weeks (range 0 – 837.3 weeks). Mean (SD) CAI at baseline was 7.5 (2.0). The groups were well matched for demographic and disease characteristics.

Clinical remission (CAI ≤ 4 at final/ withdrawal examination) was achieved in 60% of patients given BUF versus 66% given EBE, the between group difference of -6.2% (95%CI:-14.9% to 3.8%; p= 0.0236) for the PP population when adjusted for treatment

sequence. This primary analysis just demonstrated non-inferiority of BUF with EBE. The stratified PP analysis just failed the non-inferiority test with a lower boundary of the 95% CI of -15.1 (p=0.025). Non-inferiority of BUF with EBE was demonstrated for the ITT population.

Of particular note, remission rates were approximately 10% higher in patients taking foam in the morning and enema in the evening than in patients taking enema in the morning and foam in the evening. This was observed for both treatment groups and for the PP and ITT population sets. Budenofalk foam showed better efficacy in the morning and budesonide enema better efficacy in the evening. Severity of disease at baseline affected remission rates with patients with a CAI ≤ 8 at baseline achieving remission more frequently than those with a higher CAI.

BUF-6 was similar in design to BUF-9 except that it was open and had an 8 week rather than 4 week duration of treatment. This study compared BUF 2 mg daily with hydrocortisone acetate foam (HCA) 100 mg daily over 8 weeks in adults with UC proctitis or proctosigmoiditis. It was designed to demonstrate equivalent efficacy and improved safety and tolerability of BUF compared to HCA. Entry criteria were similar to those of BUF-9 except the DAI was the primary criterion for UC severity rather than the CAI. Remission at the end of treatment was defined as DAI ≤ 3. Bowel biopsies were taken to derive a Histology Index (HI) for the rectum, sigmoid, and descending colon and changes from baseline in HI were presented. The Patient's Global Impression (PGI) was also assessed.

A total of 248 patients were enrolled, 120 to receive BUD and 128 to HCA. 58% were male, 99% were Caucasian and 85% had recurrent disease. Median time since diagnosis was 46 months (range 0 – 412 months). Median duration of present episode was 5.0 weeks (range 0 – 411 weeks) and 66% had ulcerative proctosigmoiditis. Mean (SD) baseline DAI was 7.0 (2.01). 32% of patients given BUF and 29% given HCA were not included in the PP analysis due to protocol violations.

The groups were reasonably well matched for demographic and disease characteristics, though slightly more given BUF were having a first episode (22% BUF versus 15% HCA), patients given BUF had a shorter mean time since first diagnosis, longer mean duration of episodes, shorter mean time between episodes and higher use of rectal 5-ASA for the current episode at study entry (58% BUF versus 35% HCA). For the PP population clinical remission was achieved by 55% patients given BUF and by 51% given HCA, the between group difference was 4% (95% CI: -10.6 – 18.6%), not satisfying the predefined equivalence requirements. The ITT population analysis met the equivalence requirements.

Clinical remission at Day 28 was a secondary endpoint. This was achieved by 46/120 (38%) of patients given BUF and by 44/128 (34%) given HCA (ITT population) and by 38/88 (38%) given BUF and 32/91 (35%) given HCA (PP population). No statistical comparison was presented for this secondary endpoint.

Safety

The overall clinical development program involved 1035 individuals of whom 1017 were patients with documented distal UC. A total of 563 individuals received at least one dose of Budenofalk foam rectally and 120 received daily treatment at the proposed dose for 8 weeks.

No unexpected adverse events or reactions were seen in clinical trials or reported in the submitted literature. There were no withdrawal or rebound effects recorded in any of the studies and clinically relevant adrenal suppression was not observed. However, only 120 patients were exposed to BUD foam in clinical trials for the recommended maximum duration of treatment of 8 weeks. The major safety concerns were the absence of safety

data with repeated course of BUD and the lack of postmarket data for a product that has had marketing authorisations in Europe for over 5 years.

Risk management plan

Not required.

Risk-benefit analysis

Delegate considerations

The PK of the foam has not been thoroughly examined. The only steady state PK data were obtained in a small number of healthy volunteers while absorption would be expected to be higher in patients with inflammation of the distal colon. In addition the single dose radio-labelled study maximised conditions for spread of budesonide within the colon by having study subjects lie down for 4 h after administration. The prestudy colonoscopy would have emptied the colon of faecal matter which is also likely to have maximised distribution within the colon. The dose recommendations do not specify that patients lie down for 4 h after dosing so it would be anticipated that in clinical practise the spread would be somewhat less than was demonstrated in that study.

The current guideline on the development of new medicinal products for the treatment of ulcerative colitis was finalised some years after the completion of the pivotal studies to support the ulcerative colitis indication for this submission. The submission has been assessed using the recommendations of that guideline and these are more stringent than the previous guidelines, which may have been used in assessment of products for the treatment of UC that are currently registered. Relevant recommendations in the guideline include:

- Distribution of rectally applied medicinal products will have to be studied. The influence of concomitant diarrhoea on distribution should be studied as well.
- Depending on the mechanism of action, effects of mucosal inflammation on drug absorption should be addressed.
- For dose response relationship, it is recommended to use at least 3 doses.
- Phase III studies should be parallel group, randomised, double blind, placebo controlled and/ or active controlled. In general, 2 well conducted Phase III trials are needed for approval.
- For agents intended for treatment of active disease the aim of treatment should be to induce remission. This should be obtained within 4 to 8 weeks of initiation of therapy. Once obtained, remission should be maintained thoughout the duration of the induction study and for at least 4 weeks.
- Choice of comparator depends on the indication claimed (first line, second line or add-on) and the aim of the trial (induction of remission versus prevention of relapse) as well as the extent and severity of the disease.
- Choice of active control should reflect standard practises and approved indications for drugs on the market.

From the above it was noted that:

- The influence of concomitant diarrhoea on distribution of BUF has not been assessed;
- The effects of mucosal inflammation drug absorption were minimally assessed, in a single dose study that used a formulation that is not intended for registration;

- The dose response relationship was not adequately defined, relying principally on published papers of other formulations of topical budesonide, with the one study using a similar formulation to that proposed for registration, not showing a dose response relationship;
- Only one of the studies presented as pivotal was blinded. While the HCT enema that was the comparator in BUF-6 is not registered in Australia, Colifoam a product with the same composition is registered. The dose regimen for Colifoam rectal foam cream is the same as was used in that study. Colifoam is registered for topical treatment of inflammation occurring in the rectal mucosa, such as ulcerative colitis, proctosigmoiditis and granular proctitis.
- Maintenance of remission was not formally assessed. With much generosity the secondary endpoint of remission at 28 days and the primary endpoint of remission at 56 days could be considered as induction of remission followed by 4 weeks of maintenance of remission.
  - The higher remission rate at Day 56 compared with Dday 28 in Study BUC-6 strongly suggests that patients will have higher remission rates with 8 weeks rather than 4 weeks treatment for active UC.
- Neither pivotal study showed consistent non-inferiority across PP and ITT populations. This lack of consistency was contributed to by the relatively high numbers of patients who were not eligible for the PP analysis due to protocol violations.
- In Australia patients would be most likely to receive a non steroid based topical preparation initially rather than a steroid as was given in these studies.
- The effect of combination therapy with a 5-ASA preparation was not assessed, though in practise such use is likely to be more common than monotherapy foam enema.

The clinical evaluator recommended approval of the Budenofalk foam enema and noted the following regarding benefits and risks from treatment:

- a clinical remission rate (based on reduction of CAI) of approximately 50%;
- a corresponding reduction in stool frequency and blood in or on the stools; and
- a preference among patients because of its ease of handling.
- The major risks of Budenofalk foam enema in the proposed usage appear to be those associated with its glucocorticosteroid effects. The longest duration of treatment of any patient in the clinical development program was 8 weeks. However, postmarketing surveillance data suggest a low propensity for adverse drug reactions with usage in clinical settings.

While there are deficiencies in the data presented the Delegate did not consider that they were sufficient to preclude registration. The proposed indication included "*distal ulcerative colitis*" without specifying the extent of distal disease is not acceptable. The indication should specify the location of UC the product is intended to treat and that should be limited to those areas assessed in clinical trials, that is, the rectum and rectosigmoid colon. Post marketing safety data should be included in the sponsor's Pre-ACPM response.

Conclusion and recommendation

The Deleagte proposed to approve the submission to register Budenofalk foam enema containing budesonide 2 mg per 1.2 g foam enema. The indication should be amended to *Treatment of active rectal and rectosigmoid disease in ulcerative colitis.*

The advice of the ACPM was specifically requested on the following aspects of the submission:

- Should the indication specify a duration of use?
- Should registration be deferred pending a more rigorous assessment of maintenance effects?
- Should long term safety data be required prior to registration?

Enteric capsules

Quality

There were no objections to registration of Budenofalk enteric-coated capsules in respect of chemistry, manufacturing and controls to registration. The evaluator noted that the capsules contain spherical, enteric-coated beads.

Budesonide is intended to act locally in the ileum and colon. After oral administration, the systemic availability of budesonide is about 9 – 15%. Administration with food resulted in delayed absorption but did not significantly affect AUC or C_{max}. Systemic accumulation on multiple dosing of the foam enema, which has about twice the bioavailability of the oral capsule, did not occur.

Nonclinical

There were no nonclinical objections to registration. The evaluator noted that the clinical systemic exposures (plasma AUC) to budesonide at the maximal doses of Budenofalk Capsules (9 and 12 mg/day) were less than budesonide exposure from the MRHD of Entocort capsules (9 mg/day).

The low systemic availability of budesonide after oral administration is mainly due to strong first-pass metabolism, however, at least in man, part of the absorbed budesonide is already metabolised in the gut wall. This pre systemic metabolism further contributes to low systemic availability of orally administered budesonide. High first pass metabolism (about 90%) limits systemic exposure from the ingested portion of the dose. Budesonide is highly protein-bound in plasma, with approximately 90% of budesonide bound to plasma proteins in humans, rats, and dogs.

Clinical

Pharmacology

10 studies were submitted. Budesonide is rapidly and almost completely absorbed after oral administration and undergoes extensive first-pass metabolism. After oral administration of Budenofalk capsules to healthy volunteers budesonide appears in systemic circulation with a lag time of approximately 2-3 h, consistent with the pH dependent delayed release characteristics of the pellets within the capsules. C_{max} was 6 to 7 h following single doses in a 3 mg tid regimen and 5-6 h after a single 9 mg dose. Bioavailability was estimated at ~11 %. Food prolonged the lag time for appearance of budesonide in the systemic circulation by ~ 1.7 (9 mg dose) to 4.3 h (3 mg dose). Food

also decreased the mean AUC from 9.4 to 6.0 ng.h/mL for a single 3 mg dose and increased clearance from 6.0 to 12.7 L/min. The mean C_{max} decreased from 1.8 ng to

1.1 ng/mL. Budesonide has linear pharmacokinetics. No data on distribution were submitted.

Budesonide is metabolised in the wall of the small intestine and in the liver by isoenzymes within the CYP3A subfamily. After oral dosing approximately 90% of the absorbed drug is eliminated by an extensive first-pass effect. The main metabolites are 16α-hydroxy-prednisolone and 6β-hydroxybudesonide. The glucocorticoid activity of these metabolites are < 1-10% that of budesonide. Approximately 13% of a 9 mg dose of budesonide was recovered in urine as metabolites. Inter-individual variability in PK is large with the geometric CV for Cmax of 82.2%.

In subjects with active CD the pharmacokinetics of budesonide following oral ingestion of Budenofalk capsules is similar to that of healthy volunteers.

Severe hepatic impairment (Stage III/IV primary biliary cirrhosis) results in a reduction of the first-pass metabolism of budesonide and a subsequent increase in systemic exposure. Pharmacokinetics in subjects with renal impairment was not assessed.

The proposed total daily dose of 9 mg Budenofalk led to suppression of plasma cortisol levels during 8 weeks of treatment with 29% of the 3 mg tid group and 31% of the 9 mg od group having a shift from normal cortisol levels at baseline to levels below normal. The effects of Budenofalk on bone metabolism were assessed by measuring serum osteocalcin levels (a marker for bone formation) at baseline and after 8 weeks of treatment. Small reductions in osteocalcin levels and lymphocyte and granulocyte counts were seen in patients given with Budenofalk, consistent with known effects of budesonide.

Efficacy

Dose finding for CD in adults was based on a combination of published information for Entocort and limited dose finding studies with Budenofalk. The 9 mg once daily dose regimen proposed for Budenofalk is the same as that approved for Entocort. No other budesonide preparation is approved with a 3 mg tid dose regimen. Crohn's disease in adults: 6 studies using Budenofalk capsules were submitted, two Phase III, randomised double blind studies were considered pivotal (BUC-52/CDA and BUC-23) by the evaluator, the sponsor considered all 6 studies pivotal.

Study BUC-52 described in the CER, compared efficacy and safety of 9 mg Budenofalk, given either as 3 mg tid or 9 mg od, with 4.5 g mesalazine (Salofalk) given once daily to adult patients with a history of CD of at least 3 months. This study was initially planned to demonstrate superiority of Budenofalk to mesalazine however following higher than expected clinical improvement rates in the initially assessed mesalazine group it was amended to a non-inferiority study with a non-inferiority margin of -10%. This was a planned change, and was included in the protocol if remission rates with mesalazine were >40%.

The primary efficacy endpoint was clinical remission, with remission defined as Crohn's Disease Activity Index (CDAI) ≤ 150 at final (Week 8) withdrawal visit. The primary analysis was ITT, LOCF. Response rates for at least 70 and 100 points reduction in CDAI or CDAI ≤ 150 and mean change from baseline CDAI were among the secondary endpoints.

Patients with CD lesions of the upper gastrointestinal tract (GIT), symptomatic stenosis and those known to be steroid-refractory or steroid dependent from previous active episodes were excluded from study. Patients requiring concomitant or recent treatment with conventional IV, PO or rectal steroids (within the last 2 weeks); > 6 mg/d budesonide PO or > 3 g mesalazine PO (2 weeks); immunosuppressive agents, cytostatics, methotrexate or cyclosporine (3 months) or anti-TNF-α therapy (6 months) before

baseline were also excluded. On-study treatment with azathioprine or 6-mercaptopurine was permitted but was taken by only 3.3% of study patients.

Results for the primary and secondary efficacy measures are summarised in the CER. Remission was achieved by 56 (71.9%) patients given Budenofalk 3 mg tid, by 51 (67.1%) given Budenofalk 9 mg od and by 95 (62.09%) given mesalazine (ITT, LOCF). Both dose regimens of Budenofalk were combined for the statistical comparison with mesalazine. Non-inferiority of the combined Budenofalk groups with mesalazine was demonstrated (between group difference -7.39%; 95%CI -3.19% to 17.97%). Response rates and physician's global assessments were better for each Budenofalk group compared with mesalazine but no statistical analyses comparing the od and tid Budenofalk dose regimens with mesalazine were presented.

Remission rates by location of inflammation at baseline are shown in Table 61. Remission rates were broadly similar for patients with inflammation that included areas distal to the ascending colon to the overall remission rates, though no statistical analysis of remission rates for this subgroup was presented.

Table 61. Clinical remission rates (LOCF) stratified by localisation of inflammation at baseline.

		Budesonide 3 mg TID	Budesonide 9 mg OD	Total Budesonide	Mesalazine 1.5 g TID	Total
ITT analysis set						
Terminal ileum and/or ascending colon only	n/N (%)	43/62 (69.4%)	41/62 (66.1%)	84/124 (67.7%)	85/133 (63.9%)	169/257 (65.8%)
Only terminal ileum and/or ascending colon and distal colon involvement	n/N (%)	13/16 (81.3%)	10/14 (71.4%)	23/30 (76.7%)	10/20 (50.0%)	33/50 (66.0%)
PP analysis set						
Terminal ileum and/or ascending colon only	n/N (%)	39/53 (73.6%)	38/55 (69.1%)	77/108 (71.3%)	73/105 (69.5%)	150/213 (70.4%)
Only terminal ileum and/or ascending colon and distal colon involvement	n/N (%)	11/13 (84.6%)	9/13 (69.2%)	20/26 (76.9%)	9/14 (64.3%)	29/40 (72.5%)

Source: Appendix 8.1, Summary Table D.1.6
n/N: Number of patients with clinical remission / number of patients

*The above table was extracted from the Study BUC-52 report.

The second pivotal study is in the CER. *Study BUC-23* was a randomised, double-blind, controlled study comparing Budenofalk 3 mg tid with a tapering schedule of prednisone over 8 weeks (from 40 mg daily at week one reducing to 5 mg daily at Week 8) in adult patients with CD. This study included patients aged 18 to 70 years suffering from a current exacerbation of known Crohn´s disease (CDAI between 150 and 350) or with symptoms for at least 3 months in newly diagnosed patients, with localisation of disease confirmed by colonoscopy and X-ray, a negative stool culture and no current use of elemental diet, steroids or immunosuppressive agents were eligible for study entry. Concomitant use of non-steroidal anti-inflammatory drugs was not permitted.

The between group comparisons considered efficacy and steroid side effects together with 3 types of "responder" analysed as described in the CER. The primary responder analysis was of a composite of selected steroid-related side effects and CDAI score. The overall response rate (R0) did not take differences in steroid side effects into consideration and included all patients with a CDAI < 150 at end of study and in patients with a baseline CDAI < 210 a decrease in CDAI of ≥ 60. The overall response rate in the ITT population was 51.0% (n=51) in the Budenofalk group and 52.5% (n=53) in the prednisone group. Statistics were presented to show that no difference in overall response rate was demonstrated (p=0.004). For the response rate without increases in steroid-induced ADRs Budenofalk was superior to prednisone (30.0% versus 13.9%; p = 0.004).

Relevant supportive studies included 2 small dose finding studies and 2 published study reports of small company sponsored studies. Published reports of studies of Entocort (budesonide) and metaanalyses that did not specify the budesonide product used in the treatment of CD were also submitted.

Safety

A total of 858 adults were exposed to Budenofalk oral capsules in the clinical trial program, 114 in pharmacology studies, 684 in Phase II and III studies in Crohn's disease and 60 in the collagenous colitis studies as shown in the CER. Some 123 patients received Budenofalk for 6 to 8 weeks and a further 463 patients received Budenofalk for > 8 weeks.

The adverse effects of budesonide are well known and are due to the glucocorticoids. Cushingoid features occurred by Week 8 in at least 1 patient given Budenofalk to treat collagenous colitis. Serious adverse events were few and mostly attributed to worsening the underlying inflammatory bowel disease. There were no deaths on study in the pivotal studies. Four deaths were reported in exploratory studies: fatal pulmonary embolism 21 days after ceasing investigation medication; 2 deaths due to perforated colon leading to peritonitis; and 1 to intestinal carcinoma.

Study BUC-23 allowed a comparison of the glucocorticoid side effects from prednisolone and Budenofalk. The frequency of the 5 most closely steroid related effects (moon face, acne, buffalo hump, hirsuitism and skin striae) was significantly lower with Budenofalk (44% versus 67%; p = 0.0018). In that study discontinuations due to adverse events occurred in 4% of patients given Budenofalk versus 5.9% of patients given prednisolone. In comparison with mesalazine in study BUC-52/CDA Budenofalk was associated with fewer discontinuations due to treatment-related adverse effects than mesalazine (6.3% for Budenofalk 3 mg tid; 7.8% for Budenofalk 9 mg od and 15.0% for mesalazine).

Safety information was available from 163 paediatric patients with CD, 81 were reported in published papers and the remaining patients participated in company sponsored studies. No new safety issues were identified from these studies.

There was some attempt to compare growth in patients given either of the two Budenofalk dose regimens for CD by measuring height percentile at baseline and 6 months later however follow up was poor and no difference between children given the higher versus lower dose regimen was apparent.

In a published paper, striae and moon face during treatment were reported to be more common in children than adults given the same dose of oral budesonide, however these children received a higher dose/ kg than adults and they did not receive Budenofalk.

Risk management plan

Not required.

Risk-benefit analysis

The clinical evaluator had recommended approval of Budenofalk (3 mg budesonide) oral capsules for the treatment of mild to moderate active Crohn's disease of the ileum and/or colon. As noted in the adopted EU guideline, to support a first line indication in the treatment of active CD it is necessary to demonstrate that the drug has either the same or an improved risk/ benefit profile as the standard of care, which currently in the majority of cases includes glucocorticoids.

Consistent with the proposed indication, only patients with mild to moderate active disease were selected for assessment and the effect of Budenofalk on severe CD has not been examined. The development program used mesalazine and prednisolone as

comparators in the pivotal studies. Mesalazine is not a recommended first line treatment for CD either in the relevant EU guideline or in Therapeutic Guidelines Gastrointestinal[95], though 2 preparations containing mesalazine have an indication for treatment of CD (Pentasa; Salofalk). While non-inferiority of the proposed dose regimen of Budenofalk with mesalazine was demonstrated mesalazine has a better side effect profile and thus a more favourable risk/ benefit profile.

The second pivotal study (BUC-23), while showing the Budenofalk had fewer side effects than prednisolone failed to show differences in CDAI scores between Budenofalk and prednisone. This suggests, as would be expected given the comparatively low systemic absorption of budesonide, that systemic side effects were reduced with Budenofalk though only the side effects of moon face and acne were specifically examined in the statistical comparison. This study cannot be interpreted as having demonstrated equivalence or non-inferiority of Budenofalk with prednisone with respect to reductions in CDAI scores alone because it was designed as a superiority study and no statistically significant differences in CDAI scores between the groups were demonstrated.

The supportive studies were small and primarily dose finding where Budenofalk was used. Other published studies and meta analyses did not use only Budenofalk. It cannot be assumed that Budenofalk has the same activity as Entocort therefore these data add little to the assessment of efficacy of Budenofalk in the treatment of active mild to moderate CD.

The sponsor has proposed that the indication for CD should not specify CD affecting the ileum and ascending colon as in the EU and instead should refer to CD generally and noted that the clinical trials included patients with CD affecting the colon beyond the ascending colon. There was also some evidence that budesonide was present in ileostomy samples, indicating it reaches the colon however that evidence was in an abstract. The extent to which oral budesonide reaches terminal parts of the colon was not clear from the data presented. However, efficacy assessed as remission rate was demonstrated in patients with CD inflammation affecting the colon distal to the ascending colon. No visual or histological assessment of efficacy and distal colon locations in individual patients was performed.

The data support use of Budenofalk for induction of remission in patients with active mild to moderate CD. The proposed indication does not make it clear that treatment has been assessed over 8 weeks only and there are no data on maintenance in patients with mild to moderate CD.

Conclusion and recommendation

The Delegate proposed to approve Budenofalk for

> *Induction of remission in patients with mild to moderate active Crohn's disease affecting the ileum and/or the colon. (see Clinical Trials).*

The advice of the ACPM was specifically requested on whether more data on the action of Budenofalk capsules on the distal colon in patients with CD is required prior to approval of use of Budenofalk capsules for patients with CD inflammation distal to the ascending colon.

[95] Therapeutic Guidelines. Gastrointestinal. Version 5, 2011, pp 145-148.

Response from sponsor

Orphan Australia welcomed the opportunity to comment on the Delegates Overview:

Pivotal studies of efficacy and safety with Budenofalk® capsules

Both pivotal studies showing efficacy and safety of Budenofalk® capsules (BUC-23/CDA, BUC-52/CDA) were performed as randomised, double blind parallel group, multicentre trials.

Study BUC-23/CDA showed a similar efficacy of Budenofalk® capsules and prednisone with a lower incidence of the typical corticosteroid side effects moon face and acne associated with budesonide resulting in a more favourable benefit-to risk profile when compared to conventional corticosteroids.

The high rate of patients achieving remission and the favourable safety profile of Budenofalk® capsules in Study BUC-52/CDA underline the role of this preparation for patients with mild to moderate Crohn's disease.

Meta-analyses

Budenofalk® capsules and Entocort® capsules are indeed not identical preparations. However, the same active ingredient, the same recommended dose and a similar pH dependent release mechanism of the active ingredient indicate important similarities of both preparations. Therefore it appears appropriate that both preparations are included in the most relevant (Cochane-) metaanalyses on the role of oral budesonide in Crohn's disease without a major differentiation between the preparations.

Maintenance in patients with mild to moderate CD

Clinical guidelines recommend against the use of corticosteroids in maintenance treatment of inflammatory bowel disease due to the occurrence of steroid specific side effects which are associated with a long term exposure. In addition, experience with oral preparations of corticosteroids has shown that besides the safety reasons, these agents are not adequate in this indication as it seems that they are not suited to maintain a remission. Therefore, Budenofalk® capsules do not claim any indication for maintenance of remission. They should be used for induction of remission in these patients. In general, this is achieved within 8 weeks. There is no indication to use Budenofalk® capsules beyond the treatment for induction of remission.

Clarification regarding the registration status in other countries:

Please note that Budenofalk® 3 mg capsules were approved in 9 EU countries via a Mutual Recognition Procedure (MRP) with UK acting as Reference Member State and in 15 EU countries via a national procedure. Since the SmPCs are only completely harmonised in those countries taking part in the MRP some differences in the nationally approved SmPCs still exist.

Budenofalk® 9 mg granules, consisting of the same budesonide containing granules as Budenofalk® 3 mg capsules, were approved in the same 24 EU countries via a Decentralized Procedure (DCP) also with UK acting as Reference Member State.

Finally, the sponsor summarised again the key elements of its Budenofalk® 3 mg capsules submission:

- Two pivotal randomised, active controlled multicentre studies (BUC-23/CDA, BUC-52/CDA) have proven in confirmatory settings comparable efficacy and safety of 9 mg oral budesonide (Budenofalk) versus prednisone (initial dose 40 mg/day tapered) or 4.5 g oral mesalazine in patients with mild to moderately active Crohn's disease, respectively.

- Other randomised and open and pilot or dose finding studies support the findings of efficacy, safety and tolerability of Budenofalk® capsules in these patients.
- An up-to-date pharmacokinetic study (BUC-59/BIO) confirmed the findings of several early PK studies in healthy subjects and Crohn's disease patients.
- 14 years of postmarketing experience confirm and support the good safety profile noted thus far.

All studies were conducted in compliance with GCP guidelines.

Budenofalk® capsules are currently registered in 24 countries within the EEA (among them Germany, The Netherlands, Sweden, UK) and in 21 countries outside the EEA with first marketing authorisation granted in 1998.

Advisory committee considerations

Foam enema

The Advisory Committee on Prescription Medicines (ACPM) advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered this product to have an overall positive benefit–risk profile.

> *Treatment in adults of active ulcerative colitis affecting the rectum and rectosigmoid colon.*
>
> *Treatment is limited to eight weeks duration.*

The ACPM agreed with the Delegate to the proposed amendments for the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on inclusion of the following;

- A statement in the appropriate *Dosage and Administration/Clinical Trials/Precautions / Contraindications* sections of the PI and Consumer Medicine Information (CMI) to ensure that information about the absence of long term safety data, together with the clinical irrelevancy of use beyond eight weeks is clarified.

The ACPM agreed with the Delegate on the proposed conditions of registration.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Enteric capsules

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered this product to have an overall *positive benefit–risk* profile for the indication:

> *For the induction of remission in patients with mild to moderate active Crohn's disease affecting the ileum and/or ascending colon.*
>
> *Treatment is limited to no more than eight weeks in duration.*

In making this recommendation the ACPM agreed with the Delegate that more data are required to support both the use in the distal colon and the use for maintenance therapy, due to the signals of long term systemic side effects and safety risks.

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

The ACPM agreed with the Delegate on the proposed conditions of registration.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Budenofalk budesonide 3 mg enteric capsule blister pack and Budenofalk budesonide foam enema 2 mg cans for the following indications:

Budenofalk budesonide 3 mg enteric capsules

Budenofalk budesonide 3 mg enteric capsules are indicated for induction of remission in patients with mild to moderately active Crohn's disease affecting the ileum and/or the ascending colon (see Clinical Trials).

Budenofalk budesonide foam enema 2 mg

Budenofalk budesonide foam enema 2 mg is indicated in the treatment of active rectal and rectosigmoid disease in ulcerative colitis.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

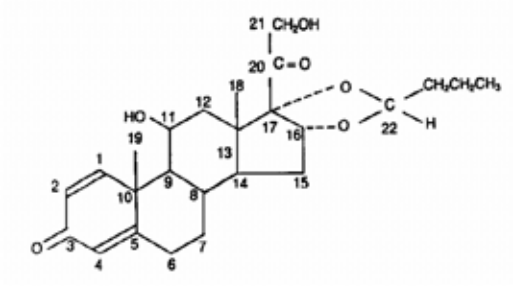
Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au
Reference/Publication #

PRODUCT INFORMATION

BUDENOFALK® Foam Enema

NAME OF THE MEDICINE



Budesonide

Proper name: Budesonide
Chemical name: 16α,17α-butylidene dioxy-11ß, 21-dihydroxy-1,4-pregnadiene-3 ,20-dione
$C_{25}H_{34}O_6$ = 430.5
CAS number : 51333-22-3

DESCRIPTION

Budesonide is a white or almost white, crystalline powder. It is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in alcohol.

BUDENOFALK foam enema contains the active ingredient budesonide. It also contains the following excipients: cetyl alcohol, emulsifying wax, purified water, disodium edetate, Steareth-10, propylene glycol, citric acid monohydrate and butane, isobutane and propane as propellants.

PHARMACOLOGY

Pharmacodynamic properties

The exact mechanism of action of budesonide in the treatment of ulcerative colitis/procto-sigmoiditis is not fully understood. Data from clinical pharmacology studies and controlled clinical trials strongly indicate that the mode of action of budesonide is predominantly based on a local action in the gut. Budesonide is a glucocorticoid with a high local anti-inflammatory effect. At a dosage of 2 mg budesonide, applied rectally, budesonide leads to practically no suppression of the hypothalamus-hypophysis-adrenal cortex axis.

BUDENOFALK 2mg foam enema investigated up to the daily dosage of 4 mg budesonide showed virtually no influence on the basal plasma cortisol level.

Pharmacokinetics

Absorption:

After oral administration, the systemic availability of budesonide is about 10%. After rectal administration the AUC is about 1.5-fold higher than in historical controls considering the identical oral budesonide dose. Peak levels are obtained after an average of 2-3 hours after administering BUDENOFALK 2mg foam enema.

Distribution:

Budesonide has a high volume of distribution (about 3 L/kg). Plasma protein binding averages 85 -90%.

Biotransformation:

Budesonide undergoes extensive biotransformation in the liver (approximately 90 %) to metabolites of low glucocorticoid activity. The glucocorticoid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1 % of that of budesonide.

Elimination:

The average elimination half-life is about 3 - 4 hours. The mean clearance rate is about 10 -15 L/min for budesonide, determined by HPLC-based methods.

Specific patient populations (liver disease):

Compromised hepatic function has an influence on the pharmacokinetics of budesonide with a reduced elimination rate and increased oral systemic availability.

BUDENOFALK foam enema

The systemic bioavailability was calculated to be 15.3 % and 13.8 % after single and multiple dosing, respectively. Comparison of data after single and multiple dosing reveals no indication for a potential accumulation of budesonide in serum.

Pharmacokinetic data are summarised in the following table for BUDENOFALK 2 mg foam after single dose and steady state dosing in 18 healthy subjects:

Table 1

Pharmacokinetic Parameters	**BUDENOFALK foam (2 mg budesonide)**	
	Day 1* Mean ± S.D. (n=18)	**Day 5** Mean ± S.D. (n=18)**
t_{max} (h)	2.14 ± 1.28	1.81 ± 0.88
C_{max} (ng/ml)	0.84 ± 0.55	0.90 ± 0.49
C_{max}/D (ng/(ml x mg))	0.42 ± 0.28	0.45 ± 0.24
$C_{average}$ (ng/ml)	-	0.36 ± 0.21
AUC_{0-12} h or AUC_{ss} (ng	4.59 ± 2.94	4.30 ± 2.58

Pharmacokinetic Parameters	**BUDENOFALK foam (2 mg budesonide)**	
	Day 1* Mean ± S.D. (n=18)	**Day 5** Mean ± S.D. (n=18)**
x h/ml)		
AUC∞ or AUC_{ss} (ng x h/ml)	5.36 ± 3.60	4.30 ± 2.58
AUC∞/D or AUC_{ss}/D (ng x h/(ml x mg))	2.68 ± 1.80	2.15 ± 1.29
k_e (h-1)	0.19 ± 0.07	-
$t_{½}$ (h)	4.05 ± 1.28	-
MRT (h)	6.36 ± 1.73	-
Cl/f (l/min)	9.33 ± 8.36	10.10 ± 5.14

* single dose on day 1; ** b.i.d. on days 2 to 5 - Healthy male volunteers (n=18)

Scintigraphic study of a single rectal dose of 99mTc-labelled budesonide 2 mg (BUDENOFALK) foam in 12 patients showed that the spread of the budesonide foam enema ranged between 11 and 40 cm (mean of 25.4 ± 10.3 cm) depending on the individual patient (this range includes from reaching the distal half of the sigmoid, to reaching the proximal third of the descending colon). The maximal spread was reached between 2 and 6 hours (mean of 4 hours) depending on the individual patient and remained relatively stable between 4 hours and 6 hours. The distal half sigmoid was reached in all patients on average after 2 hours and accounted for 27.4 % of the radiolabelled budesonide foam at 2 hours.

This study maximised conditions for spread of budesonide within the colon by having study subjects undergo a pre-study colonoscopy which would have emptied the bowel of faecal matter and by having them lie down for 4 hours after administration. It is anticipated that in clinical practise the spread would be somewhat less than was demonstrated in this study.

CLINICAL TRIALS

Study BUF-6/UCA was an active-controlled, multicentre, randomised, open-label, parallel-group trial involving 251 patients with proctitis or proctosigmoiditis. A rectally applied hydrocortisone comparator (hydrocortisone acetate 100 mg foam [Colifoam®]) was compared to budesonide 2 mg (BUDENOFALK) foam.

This study was designed to demonstrate equivalence between the two treatments with equivalence to be confirmed if the 95% CI for the between group difference in remission rate was no more than 15%. Equivalence was demonstrated only in the intent-to-treat population, not in the per-protocol population.

The primary efficacy parameter for this study was clinical remission defined as Disease Activity Index (DAI) ≤ 3 at the end of the 8-week treatment. DAI is defined as the sum of the scores of four parameters: weekly stool frequency, weekly rectal bleeding, mucosal appearance and physician's rating of disease activity.

Table 2 Clinical remission results

	Number (%) of patients with clinical remission based on DAI ≤ 3		Difference in proportion (%) of response vs. comparator	[95% CI]
	BUDENOFALK Foam Enema 2 mg o.d.	**Hydrocortisone acetate 100 mg foam o.d.**		
Analysis				
PP	48/88 (55 %)	46/91 (51 %)	4.00*; 0.99**	(-10.6, 18.6)* (-14.5, 16.5)**
ITT	63/120 (53 %)	67/128 (52 %)	0.16*; -2.63**	(-12.3, 12.6)* (-15.8, 10.5)**

LOCF; * Response is experiencing clinical remission, with 'Not recorded' taken to be "Lack of remission"; ** Response is experiencing clinical remission, excluding data classified as 'Not recorded'

INDICATIONS

BUDENOFALK foam is indicated in the treatment of active rectal and rectosigmoid disease in ulcerative colitis.

CONTRAINDICATIONS

BUDENOFALK foam is contraindicated in patients with the following:

- hypersensitivity to budesonide or any of the ingredients
- hepatic cirrhosis

PRECAUTIONS

Topical steroids have not been demonstrated to maintain remission in ulcerative colitis. Budenofalk should only be used for treatment of active ulcerative colitis. Treatment should not continue beyond 8 weeks.

Treatment with BUDENOFALK foam enema results in lower systemic steroid levels than conventional oral steroid therapy. Particular care is needed in patients who are transferred from systemic glucocorticosteroid treatment with higher systemic effect to BUDENOFALK foam enema. These patients may have adrenocortical suppression. Therefore, monitoring of adrenocortical function may be considered in these patients and their dose of systemic steroid should be reduced cautiously.

Caution is required in patients with tuberculosis, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma, cataracts, family history of diabetes, family history of glaucoma, or any other condition in which glucocorticoids may have undesirable effects.

Systemic effects of corticosteroids may occur, particularly when prescribed at high doses and for prolonged periods. Such effects may include Cushing's syndrome, adrenal suppression, growth retardation, decreased bone mineral density, cataract, glaucoma and very rarely a wide range of psychiatric/behavioural effects (see ADVERSE EFFECTS).

Corticosteroids may cause suppression of the HPA axis and reduce the stress response. When patients are subject to surgery or other stresses, supplementary systemic glucocorticoid treatment is recommended.

As with all glucocorticosteroids, some degree of adrenal suppression may occur in particularly sensitive patients, therefore, monitoring of haematological and adrenal function is strongly advised.

Infection: Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The risk of deterioration of bacterial, fungal, amoebic and viral infections during glucocorticoid treatment should be carefully considered. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked, and therefore may reach an advanced stage before being recognised.

Chickenpox: Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. If the patient is a child, parents must be given the above advice. Passive immunisation with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

Measles: Patients with compromised immunity who have come into contact with measles should, wherever possible, receive normal immunoglobulin as soon as possible after exposure.

Live vaccines: Live vaccines should not be given to individuals with chronic corticosteroid use. The antibody response to other vaccines may be diminished.

Patients with liver function disorders: Based on the experience with oral preparations of budesonide in patients suffering from late stage primary biliary cirrhosis (PBC) with hepatic cirrhosis an increased systemic availability of budesonide in all patients with severely impaired hepatic function is to be expected. However, in patients with liver disease without hepatic cirrhosis oral budesonide in daily doses of 3 mg TID was safe and well tolerated. There is no evidence that a specific dose recommendation for patients with non-cirrhotic liver diseases or only slightly impaired liver function is necessary. As the plasma levels of budesonide appear to be generally slightly higher with rectal budesonide, Budenofalk Foam Enema should be used only with caution in patients with hepatic impairment.

Effects on fertility

There are no data on the effect of budesonide on human fertility. Subcutaneous administration of budesonide to rats at doses up to 20 µg/kg/day did not affect fertility.

Use in pregnancy (Category B3)

Administration during pregnancy should be avoided unless there are compelling reasons for therapy with BUDENOFALK foam enema.

There are no data on pregnancy outcomes after rectal administration of budesonide in humans. Although data on the use of inhaled budesonide in a large number of exposed pregnancies indicate no adverse effects, the maximal concentration of budesonide in plasma is expected to be higher with rectal budesonide compared to inhaled budesonide.

In pregnant animals, administration of budesonide, like other glucocorticoids, has been shown to cause fetal death and abnormalities of fetal development (reductions in fetal/pup growth and litter size, skeletal and visceral abnormalities) The relevance of these findings to humans has not been established.

Use in lactation

Budesonide is excreted in human milk. However, only minor effects on the breast-fed infant are anticipated after Budenofalk® administration within the therapeutic range. A decision should be made whether to discontinue breastfeeding or to discontinue BUDENOFALK taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Paediatric use

BUDENOFALK foam enema is not recommended for use in children or adolescents. Long term effects, including on height and bone density have not been assessed.

Use in the elderly

The experience in elderly with BUDENOFALK foam enema is limited.

Carcinogenicity

The carcinogenic potential of budesonide has been assessed in mice and rats at respective oral doses up to 200 and 50 µg/kg/day. No oncogenic effect was noted in mice. One study showed an increased incidence of malignant gliomas in male Sprague-Dawley rats given budesonide 50 µg/kg/day; however this was not confirmed in further studies in male Sprague-Dawley and Fischer rats. In male rats dosed with 10, 25 and 50 µg/kg/day, those receiving 25 and 50 µg/kg/day showed an increased incidence of primary hepatocellular tumours; however this was also observed in rats treated with prednisolone and triamcinolone acetonide, thus indicating a class effect of corticosteroids in rats.

Genotoxicity

Budesonide had no genotoxic effects in a battery of *in vitro* and *in vivo* tests.

Effects on laboratory tests

Not known to interfere with laboratory tests or physical diagnostic agents.

INTERACTIONS WITH OTHER MEDICINES

Pharmacodynamic interactions

Cardiac glycosides:

The action of the glycoside can be potentiated by potassium deficiency.

Saluretics:

Potassium excretion can be enhanced.

Pharmacokinetic interactions

Cytochrome P450:

- CYP3A4 inhibitors:
  - Ketoconazole 200 mg orally once daily increased the plasma concentrations of budesonide (3 mg single dose) approximately 6-fold during concomitant administration. When ketoconazole was administered 12 hours after budesonide, the concentrations increased approximately 3-fold. As there are not enough data to give dose recommendations, the combination should be avoided.
    Other potent inhibitors of CYP3A4 such as ritonavir, itraconazole, clarithromycin, and grapefruit juice are also likely to cause a marked increase of the plasma concentrations of budesonide. Therefore concomitant application of budesonide should be avoided.
- CYP3A4 inducers:
  - Compounds or drugs such as carbamazepine and rifampicin, which induce CYP3A4, might reduce the systemic but also the local exposure of budesonide at the gut mucosa. An adjustment of the budesonide dose might be necessary.
- CYP3A4 substrates:
  - Compounds or drugs which are metabolized by CYP3A4 might be in competition with budesonide. This might lead to an increased budesonide plasma concentration if the competing substance has a stronger affinity to CYP3A4, or – if budesonide binds stronger to CYP3A4 – the competing substance might be increased in plasma and a dose-adaption/reduction of this drug might be required.
  - Elevated plasma concentrations and enhanced effects of corticosteroids have been reported in women also receiving oestrogens or oral contraceptives, but this has not been observed with oral low dose combination contraceptives.

ADVERSE EFFECTS

In clinical trial BUF-6/UCA involving a total of 120 patients receiving Budenofalk foam budesonide was well tolerated. The table below shows the adverse events:

Table 3 Results of study BUF-6/UCA: Summary of number and rate (%) of treatment-emergent adverse events by system organ class

Adverse event by body system	BUDENOFALK foam 2 mg N = 120	Hydrocortisone acetate 100 mg N = 128
Body as a whole		
any event	17 (14%)	24 (19%)
abdominal pain	7 (6%)	9 (7%)
headache	4 (3%)	6 (5%)
infection	4 (3%)	2 (2%)
asthenia	2 (2%)	2 (2%)
flu syndrome	2 (2%)	2 (2%)
back pain	1 (<1%)	2 (2%)
fever	1 (<1%)	2 (2%)
Digestive system		
any event	15 (13%)	14 (11%)
diarrhoea	5 (4%)	2 (2%)
gastrointestinal disorder	3 (3%)	3 (2%)
rectal disorder	2 (2%)	3 (2%)
rectal haemorrhage	2 (2%)	1 (<1%)
nausea	0	2 (2%)
Haemic and lymphatic system		
any event	4 (3%)	6 (5%)
sedimentation rate increased	3 (3%)	4 (3%)
leukocytosis	2 (2%)	1 (<1%)
Metabolic and nutritional		
any event	2 (2%)	5 (4%)
alkaline phosphatase increased	0	2 (2%)

Adverse event by body system	BUDENOFALK foam 2 mg N = 120	Hydrocortisone acetate 100 mg N = 128
peripheral oedema	0	2 (2%)
Musculoskeletal system		
any event	1 (<1%)	7 (5%)
myalgia	1 (<1%)	2 (2%)
arthralgia	0	2 (2%)
Respiratory system		
any event	3 (3%)	7 (5%)
bronchitis	0	4 (3%)
cough increased	1 (<1%)	2 (2%)
Skin and appendages		
any event	5 (4%)	4 (3%)
acne	2 (2%)	1 (<1%)
Urogenital system		
any event	2 (2%)	2 (2%)
urinary tract infection	2 (2%)	0

Undesirable effects were reported in 14% of patients in clinical trials with BUDENOFALK foam enema. Burning in the rectum or pain were common, and nausea, headache and an increase in liver enzymes were uncommon.

The following suspect adverse drug reactions presented by body system have been spontaneously reported in international post marketing surveillance as well as in clinical trials of BUDENOFALK preparations including enteric capsules and foam.

The assessment of undesirable effects is based on the following frequencies:

Very common: (≥ 1/10)
Common: (≥ 1/100 to <1/10)
Uncommon: (≥ 1/1,000 to <1/100)
Rare: (≥ 1/10,000 to < 1/1,000)
Very rare: (<1/10,000), including isolated reports.

Adverse drug reactions by frequency and system organ class (SOC):

Infections and parasitic diseases

- *Uncommon:* urinary tract infections

Blood and lymphatic system disorders

- *Uncommon:* anaemia, increase in erythrocyte sedimentation rate, leukocytosis

Metabolism and nutrition disorders

- *Uncommon:* increased appetite

Psychiatric disorders

- *Uncommon*: insomnia

Nervous system disorders

- *Uncommon:* headache, dizziness, disturbances of smell

Vascular disorders

- *Uncommon:* hypertension

Gastrointestinal disorders

- *Uncommon:* nausea, abdominal pain, dyspepsia, flatulence, abdominal complaints, anal fissure, aphthous stomatitis, frequent urge to defecate, haemorrhoids, rectal bleeding

Hepatobiliary disorders

- *Uncommon:* increase in transaminases (ALT, AST), increase in parameters of cholestasis (GGT, AP)

Skin and subcutaneous tissue disorders

- *Uncommon:* acne, increased sweating

Investigations

- *Uncommon:* increase in amylase, change in cortisol

General disorders and administration site conditions

- *Common:* burning in the rectum and pain
- *Uncommon:* asthenia, increase in body weight
- Occasionally side effects may occur which are typical for systemically acting glucocorticoids. These side effects, listed below, depend on the dosage, the period of treatment, concomitant or previous treatment with other glucocorticoids and the individual sensitivity.

Immune system disorders

- Interference with the immune response (e.g. increase in risk of infections). An exacerbation or the reappearance of extraintestinal manifestations (especially affecting skin and joints) can occur on switching a patient from the systemically acting glucocorticosteroids to the locally acting budesonide.

Metabolism and nutrition disorders

- Cushing's syndrome: moon-face, truncal obesity, reduced glucose tolerance, diabetes mellitus, sodium retention with oedema formation, increased excretion of potassium, inactivity or atrophy of the adrenal cortex, growth retardation in children, disturbance of sex hormone secretion (e.g. amenorrhoea, hirsutism, impotence)

Psychiatric disorders

- Depression, irritability, euphoria

Eye disorders

- Glaucoma, cataract

Nervous system disorders

- Pseudotumor cerebri (including papilloedema) in adolescents

Vascular disorders

- Hypertension, increased risk of thrombosis, vasculitis (withdrawal syndrome after long-term therapy)

Gastrointestinal disorders

- Stomach complaints, duodenal ulcer, pancreatitis, constipation

Skin and subcutaneous tissue disorders

- Allergic exanthema, red striae, petechiae, ecchymoses, steroid acne, delayed wound healing.
- Local skin reactions such as contact dermatitis may occur.

Musculoskeletal, connective tissue and bone disorders

- Aseptic bone necrosis (femur and head of the humerus), diffuse muscle pain and weakness, osteoporosis.

General disorders:

- Tiredness, malaise.

Some of these undesired effects were reported after long-term use of orally administered budesonide.

There are no data on the long term use of BUDENOFALK foam enema in patients with ulcerative colitis and long term use is not recommended.

Due to its local action, the risk of undesired effects of BUDENOFALK foam enema is generally lower than with systemically acting glucocorticoids.

DOSAGE AND ADMINISTRATION

For adults aged >18 years of age:

Apply one actuation of 2 mg budesonide daily. BUDENOFALK 2 mg foam enema can be applied in the morning or evening.

BUDENOFALK 2 mg foam enema should be in room temperature when applied.

The canister is first fitted with an applicator and then shaken for about 15 seconds before the applicator is inserted into the rectum as far as comfortable. Note that the dose is only sufficiently accurate when the pump dome is held downwards as vertically as possible. To administer a dose of BUDENOFALK 2 mg foam enema, the pump dome is fully pushed down and very slowly released. Following the activation the applicator should be held in position for 10-15 seconds before being withdrawn from the rectum.

The best results are obtained when the intestine is evacuated prior to administration of BUDENOFALK 2mg foam enema.

The attending physician determines the duration of use. An acute episode generally subsides after 6 to 8 weeks.

Treatment may be continued in patients showing progressive improvement, but it should not be persisted with if the response has been inadequate. Continuous treatment beyond 8 weeks has not been assessed. BUDENOFALK 2 mg foam enema should not be used after this time.

Topical steroids including BUDENOFALK have not been shown to be effective in the maintenance of remission of ulcerative colitis.

Do not use BUDENOFALK foam enema after 4 weeks of first opening the container.

OVERDOSAGE

To date, no cases of overdosage with budesonide are known. In view of the properties of budesonide contained in BUDENOFALK 2mg foam enema, an overdose resulting in toxic damage is extremely unlikely. For advice on the management of overdosage, please contact the Poisons Information Centre (telephone 13 11 26).

PRESENTATION AND STORAGE CONDITIONS

BUDENOFALK foam enema is supplied in aluminium pressurised container with metering valve together with 14 PVC applicators coated with white soft paraffin and liquid paraffin for administration of the foam and 14 plastic bags for hygienic disposal of the applicators.

Pack sizes:

Original pack with 1 pressurised container, contains at least 14 doses of 1.2 g foam enema each.*

Original pack with 2 pressurised containers, contain at least 2 x 14 doses of 1.2 g foam enema each.

(*currently not marketed)

Storage conditions:

Store below 25˚C. Do not refrigerate or freeze.

This is a pressurised container, containing flammable propellant.

Do not expose to temperature higher than 50°C, protect from direct sunlight.

Do not pierce or burn even when empty.

NAME AND ADDRESS OF THE SPONSOR

Orphan Australia Pty Ltd
(a member of the Aspen Australia group of companies)
34-36 Chandos Street
St Leonards NSW 2065
Australia.

POISON SCHEDULE OF THE MEDICINE

S4

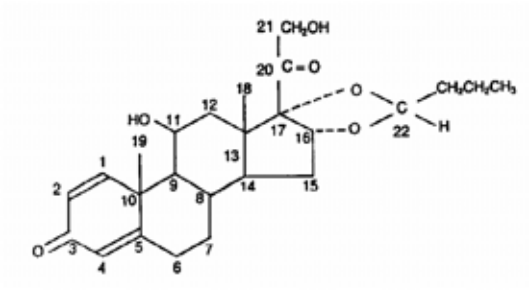
DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

12 June 2012

PRODUCT INFORMATION

BUDENOFALK® enteric capsules

NAME OF THE MEDICINE



Budesonide

Proper name: Budesonide
Chemical name: 16α,17α-butylidene dioxy-11ß, 21-dihydroxy-1,4-pregnadiene-3 ,20-dione
$C_{25}H_{34}O_6$ = 430.5
CAS number : 51333-22-3

DESCRIPTION

Budesonide is a white or almost white, crystalline powder. It is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in alcohol.

BUDENOFALK enteric capsules contain the active ingredient budesonide. They also contain the following excipients: sugar spheres (sucrose), lactose, povidone, methacrylic acid copolymer, ammonio methacrylate copolymer, triethyl citrate, purified talc, gelatin, erythrosine, sodium lauryl sulfate, titanium dioxide, iron oxide red and iron oxide black.

PHARMACOLOGY

Pharmacodynamic properties

The exact mechanism of action of budesonide in the treatment of Crohn's disease is not fully understood. The anti-inflammatory effects of budesonide, such as inhibition of the release of inflammatory mediators and suppression of the cellular immunological response, may be important. The intrinsic potency of budesonide, measured by its affinity to the glucocorticoid receptor, is about 15 times higher than the potency of prednisolone.

Data from clinical pharmacology studies and other controlled clinical trials strongly indicate that the mode of action of orally administered budesonide is predominantly based on a local action in the mucosa of the intestine and the colon due to its metabolism (by cytochrome P450 3A4) to pharmaceutically nearly inactive metabolites in the intestinal mucosa and in the liver. Doses of comparable clinical efficacy show that compared to prednisolone, BUDENOFALK has a significantly lower influence on the hypothalamo-pituitary-adrenal (HPA) axis. At the recommended dosages, BUDENOFALK has significantly less effects on morning cortisol plasma levels, 24-hour

cortisol plasma levels (AUC0-24) and 24-hour cortisol urine levels, than 20-40 mg prednisolone daily.

Pharmacokinetics

Absorption:

BUDENOFALK 3 mg enteric capsules, which contain gastric juice resistant granules, have a lag phase of 2 - 3 hours due to the specific coating of the granules. In healthy volunteers, as well as in patients with Crohn's disease, mean maximal budesonide plasma concentrations of 1-2 ng/ml were seen about 5 hours following a single 3mg oral dose of BUDENOFALK, taken before a meal. The maximal release therefore occurs in the terminal ileum and caecum, the main area of inflammation in Crohn's disease.

In ileostomy patients, release of budesonide from BUDENOFALK enteric capsules is comparable to healthy subjects or Crohn's disease patients.

Concomitant intake of food may delay release of granules from stomach by 2–3 hours, prolonging the lag phase to about 4–6 hours, without change in absorption rates.

Distribution:

Budesonide has a high volume of distribution (about 3 L/kg). Plasma protein binding averages 85–90 %.

Biotransformation:

Budesonide undergoes extensive biotransformation in the intestinal mucosa and in the liver (approximately 90%) to metabolites of low glucocorticoid activity. The glucocorticoid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1 % of that of budesonide.

Metabolism:

Budesonide is mainly metabolised via cytochrome P450 3A4 in the intestinal mucosa and in the liver.

Elimination:

The average elimination half-life is about 3–4 hours. The systemic availability in healthy volunteers, as well as in fasting patients with Crohn's disease, is about 9–13 %. The clearance rate is about 10–15 L/min for budesonide, determined by HPLC-based methods.

Specific patient populations (liver diseases):

Dependent on the type and severity of liver diseases and due to the fact that budesonide is metabolised by CYP3A4 in the liver, the metabolism of budesonide may be decreased in patients with liver diseases. Therefore, the systemic exposure of budesonide may be increased in patients with impaired hepatic function. With improving liver function and disease, metabolism of budesonide will normalize.

The bioavailability of budesonide has been found to be significantly higher in patients with liver cirrhosis (PBC Stage IV) than in patients with liver diseases without cirrhosis (PBC Stage I/II). Following repeated administration of budesonide 3 x 3 mg daily the

AUC, on average, was threefold greater in patients with liver cirrhosis (late-stage PBC), than in patients with early-stage PBC.

BUDENOFALK enteric capsules

The mean peak plasma concentration of budesonide after a single dose of 9 mg budesonide (BUDENOFALK 3 x 3 mg capsules) was 1.73 ± 1.40 ng/mL at a median T_{max} of 5.00 hours. For the metabolite 6-β-hydroxy-budesonide, the mean plasma concentration and T_{max} were similar to budesonide (2.80 ± 1.26 ng/mL, and 5.5 hours, respectively). Higher concentrations were observed for the major metabolite 16-α-hydroxyprednisolone: the mean C_{max} of 23.11 ng/ml occurred after a median T_{max} of 5.45 hours. Of the 9 mg dose, 11.58% could be recovered in urine in form of 16-α-hydroxyprednisolone and 1.46% in form of 6-β-hydroxy-budesonide.

Pharmacokinetic data are summarised in the following table for BUDENOFALK enteric capsules (3 x 3 mg budesonide once daily) in 18 healthy subjects:

Table 1

Pharmacokinetic Parameters	**BUDENOFALK enteric capsules (3 x 3 mg budesonide once daily)**		
	Budesonide Mean* [SD]	**16-α-hydroxy-prednisolone Mean* [SD]**	**6-β-hydroxy-budesonide Mean* [SD]**
Cmax [ng/mL]	1.73 [1.40]	23.11 [15.39]	2.80 [1.26]
tmax [hr]	5.00^ [2.15]	5.45^ [1.54]	5.50^ [1.71]
t1/2 [hr]	3.37 [1.70]	2.97 [1.58]	5.37 [2.22]
AUC(∞) [hr*ng/mL]	10.25 [6.03]	119.23 [59.10]	25.46 [10.66]
AUC last [hr*ng/mL]	8.25 [6.18]	105.50 [60.62]	22.66 [8.83]

* Geometric means

^ nonparametric evaluation, median

Pharmacokinetic data are summarised in the following table for BUDENOFALK enteric capsules (3 mg budesonide three times daily) in 12 healthy subjects:

Table 2

	BUDENOFALK enteric capsules (3 mg budesonide three times daily)	
	Budesonide Mean [SD]	**Budesonide and metabolites Mean [SD]**
C_{max} 1 [ng/mL]	1.03 [0.45]	1.89 [1.03]
C_{max} 2 [ng/mL]	0.82 [0.33]	1.82 [0.51]
C_{max} 3 [ng/mL]	0.70 [0.38]	0.55 [0.18]

	BUDENOFALK enteric capsules (3 mg budesonide three times daily)	
	Budesonide Mean [SD]	**Budesonide and metabolites Mean [SD]**
t_{max} 1 [hr]	5.8 [1.6]	5.2 [1.6]
t_{max} 2 [hr]	14.7 [1.5]	15.1 [1.5]
t_{max} 3 [hr]	23.5 [0.9]	23.0 [1.3]
$t_{1/2}$ [hr]	2.6 [1.3]	3.0 [0.7]
$AUC_{(\infty)}$ [hr*ng/mL]	13.5 [4.9]	29.0 [9.1]

CLINICAL TRIALS

In a multicentre, randomised, controlled study (BUC-23/CDA) the efficacy and safety of BUDENOFALK enteric capsules given at a dose of 3 mg TID was compared with a decreasing dose of prednisone (from 40mg daily, reducing to 5 mg daily) over 8 weeks.

The Crohn's Disease Activity Index (CDAI) was the main clinical assessment for determining efficacy. The CDAI is a validated index based on subjective aspects rated by the patient (frequency of liquid or very soft stools, abdominal pain rating and general well-being) and objective observations (number of extra-intestinal symptoms, need for anti-diarrhoeal drugs, presence of abdominal mass, body weight and haematocrit).

The primary analysis was of a composite of selected steroid-related side effects and CDAI score. Three types of responder were assessed. These were defined as:

- "R1" responder – response without the occurrence of either "moon face" or "acne" (considered to be the main steroid-induced ADRs)
- "R2" responder – response associated with the occurrence of at least one steroid-induced ADR
- "R0" responder – overall response (R1 or R2 response).

The overall response rate (R0) did not take differences in steroid side effects into consideration and included all patients with a CDAI < 150 at end of study and, in patients with a baseline CDAI < 210, a decrease in CDAI of ≥ 60.

Table 3: Clinical remission rates after 8 weeks of study treatment (ITT and PP analysis sets; study BUC-23/CDA) in adult patients with active Crohn's disease

Analysis set/Remission category	**Budesonide n (%)**	**Prednisone n (%)**	**Treatment comparison [a] (p-value)**
ITT analysis set	**N=100**	**N=101**	
R1 remission (primary variable)	30 (30.0%)	14 (13.9%)	0.004
R2 remission	21 (21.0%)	39 (38.6%)	n.a.

Analysis set/Remission category	**Budesonide n (%)**	**Prednisone n (%)**	**Treatment comparison [a] (p-value)**
R0 remission	51 (51.0%)	53 (52.5%)	n.a.
PP analysis set	**N=84**	**N=87**	
R1 remission (primary variable)	28 (33.3%)	12 (13.8%)	0.002
R2 remission	19 (22.6%)	36 (41.4%)	n.a.
R0 remission	47 (56.0%)	48 (55.2%)	n.a.

[a] Fisher's exact test, 1-sided

In a double-blind, randomised, multicentre study (BUC-52/CDA) the efficacy and safety of a 8 weeks treatment with BUDENOFALK enteric capsules 9 mg/day (3 mg capsules three times daily or 3 x 3 mg capsules once daily) was compared to Salofalk tablets 4.5g/day (3 x 500 mg tablets three times daily) in the therapy of active Crohn's disease.

The primary efficacy variable was clinical remission of Crohn's disease defined as CDAI score of ≤ 150 from baseline at the final visit (week 8) or at the withdrawal visit. Results showed that BUDENOFALK 3 mg enteric capsules are non-inferior to mesalazine in the treatment of active Crohn's disease (non-inferiority margin -10%). No significant difference in remission rate was observed for the 2 budesonide dosage regimens (budesonide 3 mg three times daily compared to budesonide 9 mg once daily).

Table 4: Clinical remission rates at the final visit (Week 8) or withdrawal visit: Comparison of budesonide with mesalazine (LOCF; ITT and PP analysis sets; study BUC-52/CDA) in adult patients with active Crohn's disease

	Total Budesonide n (%)	**Mesalazine 1.5 g TID n (%)**	**Difference in proportions: Total Budesonide vs. Mesalazine 1.5 g TID (95% CI), p-value [a]**
ITT	107 (69.48%) (N=154)	95 (62.09%) (N=153)	7.39% [b] (–3.19% to 17.97%) p=0.0013 [a]
PP	97 (72.39%) (N=134)	82 (68.91%) (N=119)	3.48% [b] (–7.77% to 14.73%) p=0.0139 [a]

[a] Farrington-Manning χ^2 test for shifted hypotheses, non-inferiority margin = -10%, 1-sided overall p-value of 3-stage group sequential design.

[b] Difference in proportions = proportion of total budesonide - proportion of mesalazine

n (%): number (percent) of patients in remission

Table 5: Clinical remission rates at the final visit (Week 8) or withdrawal visit: Comparison of budesonide regimens (LOCF; ITT and PP analysis sets; study BUC-52/CDA) in adult patients with active Crohn's disease

	Budesonide 3 mg TID n (%)	**Budesonide 9 mg QD n (%)**	**Total Budesonide n (%)**	**Difference in proportions: Budesonide 9 mg QD vs. Budesonide 3 mg TID (95% CI), p-value [a]**
ITT	56 (71.79%) (N=78)	51 (67.11%) (N=76)	107 (69.48%) (N=154)	–4.69% [b] (–19.23% to 9.85%) p=0.5275 [a]
PP	50 (75.76%) (N=66)	47 (69.12%) (N=68)	97 (72.39%) (N=134)	–6.64% [b] (–21.72% to 8.44%) p=0.3901 [a]

[a] 2-sided χ^2 test

[b] Difference in proportions = proportion of budesonide 9 mg QD - proportion of budesonide 3 mg TID

n (%): number (percent) of patients in remission

TID, three times daily; QD, once daily

Results of the studies show that BUDENOFALK enteric capsules are well tolerated in patients with active Crohn's disease (see ADVERSE EFFECTS).

INDICATIONS

BUDENOFALK enteric capsules are indicated for:

- Induction of remission in patients with mild to moderately active Crohn's disease affecting the ileum and/or the ascending colon (see CLINICAL TRIALS).

CONTRAINDICATIONS

BUDENOFALK enteric capsules are contraindicated in patients with the following:

- hypersensitivity to budesonide or any of the ingredients
- hepatic cirrhosis

PRECAUTIONS

Treatment with BUDENOFALK 3mg does not appear useful in patients with Crohn´s disease affecting the upper gastro-intestinal tract. Extraintestinal symptoms, e.g. involving the skin, eyes or joints, are unlikely to respond to Budenofalk 3mg because of its local action.

Treatment with BUDENOFALK enteric capsules results in lower systemic steroid levels than conventional oral steroid therapy. Particular care is needed in patients who are transferred from systemic glucocorticosteroid treatment with higher systemic effect to BUDENOFALK enteric capsules. These patients may have adrenocortical suppression. Therefore, monitoring of adrenocortical function may be considered in these patients and their dose of systemic steroid should be reduced cautiously.

Caution is required in patients with tuberculosis, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma, cataracts, family history of diabetes, family history

of glaucoma, or any other condition in which glucocorticoids may have undesirable effects.

Systemic effects of corticosteroids may occur, particularly when prescribed at high doses and for prolonged periods. Such effects may include Cushing's syndrome, adrenal suppression, growth retardation, decreased bone mineral density, cataract, glaucoma and very rarely a wide range of psychiatric/behavioural effects (see ADVERSE EFFECTS).

Corticosteroids may cause suppression of the HPA axis and reduce the stress response. When patients are subject to surgery or other stresses, supplementary systemic glucocorticoid treatment is recommended.

As with all glucocorticosteroids, some degree of adrenal suppression may occur in particularly sensitive patients, therefore, monitoring of haematological and adrenal function is strongly advised.

Infection: Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The risk of deterioration of bacterial, fungal, amoebic and viral infections during glucocorticoid treatment should be carefully considered. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked, and therefore may reach an advanced stage before being recognised.

Chickenpox: Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. If the patient is a child, parents must be given the above advice. Passive immunisation with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

Measles: Patients with compromised immunity who have come into contact with measles should, wherever possible, receive normal immunoglobulin as soon as possible after exposure.

Live vaccines: Live vaccines should not be given to individuals with chronic corticosteroid use. The antibody response to other vaccines may be diminished.

Patients with liver function disorders: Based on the experience with patients suffering from late stage primary biliary cirrhosis (PBC) with hepatic cirrhosis an increased systemic availability of budesonide in all patients with severely impaired hepatic function is to be expected. However, in patients with liver disease without hepatic cirrhosis budesonide in daily doses of 3 mg TID was safe and well tolerated. There is no evidence that a specific dose recommendation for patients with non-cirrhotic liver diseases or only slightly impaired liver function is necessary.

Others: BUDENOFALK enteric capsules contain lactose and sucrose. Patients with rare hereditary problems of galactose or fructose intolerance, glucose-galactose malabsorption, sucrase-isomaltase insufficiency, the Lapp lactase deficiency or the congenital lactase deficiency should not take this medicine.

Effects on fertility

There are no data on the effect of budesonide on human fertility. Subcutaneous administration of budesonide to rats at doses up to 20 µg/kg/day did not affect fertility.

Use in pregnancy (Category B3)

Administration during pregnancy should be avoided unless there are compelling reasons for therapy with BUDENOFALK capsules.

There are few data on pregnancy outcomes after oral administration of budesonide in humans. Although data on the use of inhaled budesonide in a large number of exposed pregnancies indicate no adverse effects, the maximal concentration of budesonide in plasma is expected to be higher with oral budesonide compared to inhaled budesonide.

In pregnant animals, administration of budesonide, like other glucocorticoids, has been shown to cause fetal death and abnormalities of fetal development (reductions in fetal/pup growth and litter size, skeletal and visceral abnormalities). The relevance of these findings to humans has not been established.

Use in lactation

Budesonide is excreted in human milk. However, only minor effects on the breast-fed infant are anticipated after BUDENOFALK intake within the therapeutic range. A decision should be made whether to discontinue breastfeeding or to discontinue BUDENOFALK taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Paediatric use

BUDENOFALK is not recommended for use in children or adolescents. Long term effects, including on height and bone density have not been assessed.

Use in the elderly

The experience in elderly with BUDENOFALK enteric capsules is limited.

Carcinogenicity

The carcinogenic potential of budesonide has been assessed in mice and rats at respective oral doses up to 200 and 50 µg/kg/day. No oncogenic effect was noted in mice. One study showed an increased incidence of malignant gliomas in male Sprague-Dawley rats given budesonide 50 µg/kg/day; however this was not confirmed in further studies in male Sprague-Dawley and Fischer rats. In male rats dosed with 10, 25 and 50 µg/kg/day, those receiving 25 and 50 µg/kg/day showed an increased incidence of primary hepatocellular tumours; however this was also observed in rats treated with prednisolone and triamcinolone acetonide, thus indicating a class effect of corticosteroids in rats.

Genotoxicity

Budesonide had no genotoxic effects in a battery of *in vitro* and *in vivo* tests.

Effects on laboratory tests

Not known to interfere with laboratory tests or physical diagnostic agents.

INTERACTIONS WITH OTHER MEDICINES

Pharmacodynamic interactions

Cardiac glycosides:

The action of the glycoside can be potentiated by potassium deficiency.

Saluretics:

Potassium excretion can be enhanced.

Pharmacokinetic interactions

Cytochrome P450:

- *CYP3A4 inhibitors:*
  - Ketoconazole 200 mg orally once daily increased the plasma concentrations of budesonide (3 mg single dose) approximately 6-fold during concomitant administration. When ketoconazole was administered 12 hours after budesonide, the concentrations increased approximately 3-fold. As there are not enough data to give dose recommendations, the combination should be avoided.
  - Other potent inhibitors of CYP3A4 such as ritonavir, itraconazole, clarithromycin, and grapefruit juice are also likely to cause a marked increase of the plasma concentrations of budesonide. Therefore concomitant intake of budesonide should be avoided.

- *CYP3A4 inducers:*
  - Compounds or drugs such as carbamazepine and rifampicin, which induce CYP3A4, might reduce the systemic but also the local exposure of budesonide at the gut mucosa. An adjustment of the budesonide dose (using e.g. budesonide 3mg capsules) might be necessary.

- *CYP3A4 substrates:*
  - Compounds or drugs which are metabolized by CYP3A4 might be in competition with budesonide. This might lead to an increased budesonide plasma concentration if the competing substance has a stronger affinity to CYP3A4, or – if budesonide binds stronger to CYP3A4 – the competing substance might be increased in plasma and a dose-adaption/reduction of this drug might be required.
  - Elevated plasma concentrations and enhanced effects of corticosteroids have been reported in women also receiving oestrogens or oral contraceptives, but this has not been observed with oral low dose combination contraceptives.
  - Cimetidine at recommended doses in combination with budesonide has a small but insignificant effect on pharmacokinetics of budesonide. Omeprazole has no effect on the pharmacokinetics of budesonide.

Steroid-binding compounds:

In theory, potential interactions with steroid-binding synthetic resins such as cholestyramine, and with antacids cannot be ruled out. If given at the same time as BUDENOFALK enteric capsules, such interactions could result in a reduction in the

effect of budesonide. Therefore these preparations should not be taken simultaneously, but at least two hours apart.

ADVERSE EFFECTS

BUDENOFALK is generally well tolerated. In clinical studies most adverse events were of mild to moderate intensity and of a non-serious character.

In two clinical trials involving 256 patients with acute Crohn's disease, budesonide was well tolerated. The table below shows the adverse events that occurred in at least 10% of patients in any of the two clinical trials included:

Table 6

Adverse event	BUC-23/CDA		BUC-52/CDA		
	Budenofalk 3 mg TID (n = 100) n (%)	Prednisone (n = 101) n (%)	Budenofalk 9mg QD (n = 77) n (%)	Budenofalk 3 mg TID (n = 79) n (%)	Salofalk 1.5 g TID (n = 153) n (%)
Abdominal pain	21 (21%)	16 (15.8%)	2 (2.6%)	1 (1.3%)-	8 (5.2%)
Epigastric pain / upper abdominal pain	4 (4%)	10 (9.9%)	-	-	-
Headache	-	-	8 (10.4%)	6 (7.6%)	19 (12.4%)
Viral infection	-	-	8 (10.4%)	3 (3.8%)	5 (3.3%)
Diarrhoea/soft stools	12 (12%)	7 (6.9%)	-	-	-

QD, once daily; TID, three times daily

The following undesirable effects and frequencies of Budenofalk 3 mg enteric capsules have been spontaneously reported:

Very rare (< 1/10,000), including isolated reports:

- *Metabolism and nutritional disorders:* oedema of legs, Cushing's syndrome
- *Nervous system disorders:* Pseudotumor cerebri (including papilloedema) in adolescents
- *Gastrointestinal disorders:* Constipation
- *Musculoskeletal and connective tissue disorders:* diffuse muscle pain and weakness, osteoporosis
- *General disorders:* tiredness, malaise

Some of the undesired effects were reported after long-term use.

Occasionally side effects may occur which are typical for systemic glucocorticoids. These side effects depend on the dosage, the period of treatment, concomitant or previous treatment with other glucocorticoids and the individual sensitivity.

Clinical studies showed that the frequency of glucocorticosteroid associated side effects is lower with Budenofalk enteric capsules (approx. by half) than with oral treatment of equivalent dosages of oral prednisolone.

Immune system disorders:

Interference with the immune response (e.g. increase in risk of infections).

An exacerbation or the reappearance of extraintestinal manifestations (especially affecting skin and joints) can occur on switching a patient from systemically acting glucocorticoids to the locally acting budesonide.

Metabolism and nutrition disorders:

Cushing's syndrome: moon-face, truncal obesity, reduced glucose tolerance, diabetes mellitus, sodium retention with oedema formation, increased excretion of potassium, inactivity or atrophy of the adrenal cortex, growth retardation in children, disturbance of sex hormone secretion (e.g. amenorrhoea, hirsutism, impotence)

Psychiatric disorders:

- Depression, irritability, euphoria.
- In addition, very rarely a wide range of psychiatric/behavioural effects may occur.

Eyes disorders:

- Glaucoma, cataract

Vascular disorders:

- Hypertension, increased risk of thrombosis, vasculitis (withdrawal syndrome after long-term therapy)

Gastro intestinal disorders:

- Stomach complaints, gastroduodenal ulcer, pancreatitis

Skin and subcutaneous tissue disorders:

- Allergic exanthema, red striae, petechiae, ecchymosis, steroid acne, delayed wound healing, contact dermatitis

Musculoskeletal, connective tissue and bone disorders:

- Aseptic necrosis of bone (femur and head of the humerus)

DOSAGE AND ADMINISTRATION

Adults and the elderly:

For acute Crohn's disease (for 8 weeks):

- 9 mg budesonide once daily in the morning, or
- 3 mg budesonide 3 times daily (morning, midday and evening)

Safety and Efficacy of BUDENOFALK enteric capsules have been assessed for up to 8 weeks in adults. Continuous treatment beyond 8 weeks is not recommended. Patients may receive episodic treatment.

At discontinuation

At the end of treatment, the dosage should be tapered gradually, to avoid the possibility of insufficient function of the cortex of the suprarenal gland.

In the first week, the dosage should be reduced to two capsules daily, one in the morning, one in the evening. In the second week, only one capsule should be taken in the morning. After two weeks of gradual dose reduction, treatment can be discontinued.

Method of administration

The enteric capsules may be taken whole, without chewing or crushing, about 30 minutes before meals with sufficient water. Patients with difficulty swallowing the capsules may open the capsule and administer the granules without chewing or crushing and with plenty of liquid.

OVERDOSAGE

Acute overdose with BUDENOFALK enteric capsules is unlikely to result in clinical problems. For advice on the management of overdosage, please contact the Poisons Information Centre (telephone 13 11 26).

PRESENTATION AND STORAGE CONDITIONS

BUDENOFALK 3 mg enteric capsules are presented as pink opaque, oblong hard gelatin capsules. Each enteric capsule contains 3 mg of budesonide. Enteric capsules are supplied in blister strips with aluminum foil backing.

Cartons of 9*, 45* and 90 are available.

(*currently not marketed)

Store below 25˚C.

NAME AND ADDRESS OF THE SPONSOR

Orphan Australia Pty Ltd
(a member of the Aspen Australia group of companies)
34-36 Chandos Street
St Leonards NSW 2065
Australia.

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

12 June 2012

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