Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Adalimumab (rch)

Proprietary Product Name: Humira

Sponsor: AbbVie Pty Ltd

July 2016

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 is responsible for regulating medicines and medical devices.
- The 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 <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (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; it provides 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

ADR

Common abbreviations

Abbreviation	Meaning
AAA	Anti-adalimumab antibody
ACPM	Advisory Committee on Prescription Medicines
AE	Adverse event
AESI	Adverse event of special interest
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
ASA	Australian specific annex
AN	Abscess and inflammatory nodule
AN25	At least 25% reduction in abscess and inflammatory nodule count relative to Baseline
AN50	At least 50% reduction in abscess and inflammatory nodule count relative to Baseline
AN75	At least 75% reduction in abscess and inflammatory nodule count relative to Baseline
AN100	100% reduction in abscess and inflammatory nodule count relative to Baseline
AS	Ankylosing spondylitis
BMI	Body mass index
CD	Crohn's disease
CMH	Cochran Mantel Haenszel
CMI	Consumer Medicine Information
DLQI	Dermatology Life Quality Index
EU	European Union
HiSCR	Hidradenitis Suppurativa Clinical Response
HIV	Human immunodeficiency virus
HS	Hidradenitis suppurativa
HS–PGA	Hydradenitis suppurative Physician`s Global Assessment

Abbreviation	Meaning
HSTCL	Hepatosplenic T–cell lymphoma
IBD	International birth date
ITT	Intent to treat
JIA	Juvenile idiopathic arthritis
LOCF	Last observation carried forward
LOR	Loss of response
NMSC	Non–melanoma skin cancer
NR	Non–responder
NRI	Non–responder imputation
Nr–ax SpA	Non–radiographic axial spondylarthritis
PBO	Placebo
PedERA	Paediatric enthesitis related arthritis
PGA	Physician's Global Assessment
PI	Product Information
PK	Pharmacokinetic
Ps	Psoriasis
PsA	Psoriatic arthritis
PY	Patient year
qw	Weekly
Q2w	Every other week
RA	Rheumatoid arthritis
SAE	Serious adverse event
SmPC	Summary of product characteristics
SpA	Spondylarthritis
TEAE	Treatment emergent adverse event

Abbreviation	Meaning
TESAE	Treatment emergent serious adverse event
TNF	Tumor necrosis factor
UC	Ulcerative colitis
US	United States
Wk	Week

I. Introduction to product submission

Submission details

Type of submission:	Major variation; extension of indications
Decision:	Approved
Date of decision:	06 April 2016
Date of entry onto ARTG	08 April 2016
Active ingredient:	Adalimumab (rch)
Product name:	Humira
Sponsor's name and address:	AbbVie Pty Ltd Locked Bag 5029 Botany NSW 1455
Dose form:	Solution for injection
Strengths:	10, 20 and 40 mg
Containers:	Pre–filled syringe (10, 20 and 40 mg), vial (40 mg) and pen (40 mg).
Pack sizes:	Prefilled syringe 10 mg and 20 mg as a pack of 2 syringes; and 40 mg as a pack containing either 1, 2, 3, 4 or 6 syringes. Humira 40 mg solution prefilled pen: a pack containing either 1, 2 , 3, 4 or 6 syringes Humira 40 mg solution (vial): Pack containing 1 vial
Approved therapeutic use:	*Humira is indicated for the treatment of moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional systemic hidradenitis suppurativa therapy.*
Route of administration:	Subcutaneous (SC)
Dosage:	160 mg at Day 1 (given as 4 40 mg injections in one day or as two 40 mg injections per day for two consecutive days) followed by 80mg two weeks later at Day 15 (given as two 40mg injections in one day). Two weeks later (day 29) continued with a dose of 40 mg every week.
ARTG numbers:	238700, 216038, 199412, 199411, 199410, 95779

Product background

This AusPAR describes the application by Abbvie Pty Ltd (the sponsor) to register Humira (adalimumab (rch)) for the indication:

Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.

Humira (adalimumab (rch)) is a fully human immunoglobulin G1(IgG1) type recombinant monoclonal antibody against tumor necrosis factor (TNF)–α. It binds to TNF and neutralises the biologic function of TNF by blocking its interaction with the p55 and p75 cell surface receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF. Humira is produced in a Chinese hamster ovary (CHO) cell expression system.

The currently approved indications in Australia are rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC) and psoriasis (Ps).

Hidradenitis suppurativa (HS) is a chronic follicular occlusive disease involving the follicular portion of folliculo–pilo–sebaceous units[1]. Primary sites are intertriginous skin areas of the axillary, groin, perianal, perineal and inframammary regions. Clinical manifestations range from recurrent inflamed nodules and abscesses through to draining sinus tracts and bands of severe scarring. Pain, malodour, drainage and disfigurement contribute to a profound psychosocial impact. Onset is usually between puberty and 40 years. Incidence is higher in women. There is a strong correlation with smoking, and a weaker correlation with obesity.

The Hurley staging system refers to three stages of severity based on the presence and extent of sinus tracts and scarring (Table 1). The Hidradenitis Suppurativa Physicians Global Assessment scale (HS–PGA) refers to five stages (from no skin disease to very severe symptoms) based on the presence or absence of abscesses, draining fistulas, inflammatory and non–inflammatory nodules (Table 2).

Table 1: Hurley stages

Stage	Description
I	Abscess formation (single or multiple) without sinus tracts and cicatrisation.
II	Recurrent abscesses with tract formation and cicatrisation; single or multiple, widely separated lesions.
III	Diffuse or near–diffuse involvement or multiple interconnected tracts and abscesses across entire areas.

Annals of Internal Medicine, Vol. 157, No12, 18 Dec 2012.

Table 2: Hidradenitis suppurativa physicians global assessment scale

Rating	Description
Clear	0 abscesses, 0 draining fistulas, 0 inflammatory nodules and 0 non-inflammatory nodules
Minimal	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and presence of non–inflammatory nodules

[1] Margesson LJ and Danby FW: Pathogenesis, clinical features, and diagnosis of hidradenitis suppurativa (acne inversa). From Up–to–date Topic 5575 Version 18.0 Topic last updated Sep 29, 2015.

Rating	Description
Mild	0 abscesses, 0 draining fistulas, and 1 to4 inflammatory nodules *or* 1 abscess or draining fistula and 0 inflammatory nodule
Moderate	0 abscesses, 0 draining fistulas, and ≥ 5 inflammatory nodules *or* 1 abscess or draining fistula ≥ 1 inflammatory nodule *or* 2 to 5 abscesses or draining fistulas and ≤ 10 inflammatory nodules
Severe	2 to 5 abscesses or draining fistulas and ≥ 10 inflammatory nodules
Very severe	≥ 5 abscesses or draining fistulas

Annals of Internal Medicine, Vol. 157, No12, 18 Dec 2012.

Goals of treatment include:

- To prevent the formation of new lesions and thus reduce the extent and progression of the disease.
- To treat new lesions quickly and effectively to prevent development of chronic sinuses.
- To eliminate existing nodules and sinus tracts to limit or prevent scar formation.

Current treatments can involve topical and systemic medication, surgery (for example for nodules, sinus tracts and scarring) and behavioural/lifestyle approaches (for example smoking cessation and weight management). Medicines include antibiotics and hormonal therapies; in those who do not respond to these approaches, biological therapies and oral retinoids can be considered.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 10 December 2003.

At the time the TGA considered this application, a similar application had been approved in the European Union (EU) in June, 2015 for:

> *adults with active moderate to severe hidradenitis suppurativa (acne inversa), who have failed to respond to conventional systemic treatments*.

Submission dates for the HS dossier in EU, US and Canada are included in Table 3.

Table 3: Submission and approval dates for HS dossier in the EU, US and Canada.

Country or Region	Submission date	Status	Approved indications
EU	11 November 2014	Approved on 29 July 2015	Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with inadequate response to conventional systemic HS therapy.

Country or Region	Submission date	Status	Approved indications
US	10 November 2014	Approved on 09 September 2015	Humira is indicated for the treatment of moderate to severe hidradenitis suppurativa.
Canada	14 January 2015	Approved on 31 December 2015	Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa in adult patients, who have not responded to conventional therapy (including systemic antibiotics).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

Hidradenitis suppurativa (HS) is a debilitating, chronic inflammatory follicular disease characterised by the formation of recurrent abscesses, inflammatory nodules, and fistulas. It mainly involves skin regions with apocrine glands such as axillae, groins, perineal and perianal areas, and submammary areas. Lesions are often painful and result in malodorous discharge. Complications include excessive scarring and fibrosis potentially leading to contractures and limitations in mobility, as well as anal, urethral, and rectal strictures. Other comorbidities associated with HS include anaemia, secondary infection, malignancy (such as non–melanoma skin cancer [NMSC]), depression, and anxiety. These disease sequelae result in significant reduction of health related quality of life in affected individuals.

The estimated prevalence of HS is approximately 1%. The disease onset is typically in the second and third decade of life and is rare in prepubertal children. Women are affected

more commonly than men (female/male ratio approximately 2:1). Predisposing factors include obesity and cigarette smoking. The diagnosis is usually established based on the clinical presentation. Several disease severity scores have been developed, with the most commonly used being the three–stage Hurley score (Table 1).

Regarding management, the general lack of large randomised controlled studies limits therapeutic options for HS, which include both medical and surgical treatments. Medical treatment options include topical and systemic antibiotics (clindamycin and rifampicin alone or in combination, tetracyclines), oral anti androgen agents in women, dapsone and/or isotretinoin. More recently, the use of systemic anti TNF therapy (infliximab, etanercept, adalimumab) has shown promising results. Surgical options include radical excisions and deroofing as well as laser ablation (CO_2 and Nd:YAG lasers). Most of the described treatments are based on small case series, and no widely accepted therapeutic guidelines are available for HS.

The sponsors Clinical Overview states '*Given that (a) the abscesses and inflammatory nodules of HS cause pain and malodour, and may culminate in scar formation; (b) there are no approved medical therapies for the abscesses and inflammatory nodules of HS; and (c) surgical and laser therapies can be associated with significant post–procedure morbidity and uncertain long–term disease control, there is a significant unmet medical need for therapies to treat this condition. Based on the current treatment options and unmet medical need, sponsor considers that adalimumab has the potential to provide safe and effective therapy for moderate to severe HS and thus conducted a clinical development program for this indication.*'

Contents of the clinical dossier

For HS

The clinical dossier documented a development program of pharmacokinetic and immunogenicity, dose–finding, pivotal and other clinical trials relating to the proposed extension of indications.

The submission contained the following clinical information:

- 2 pivotal efficacy/safety studies (M11–313, M11–810, M12–555)
- 1 Phase II efficacy/safety study (M10–467)
- 3 separate pharmacokinetic reports derived from the pivotal efficacy/safety studies
- Integrated Summary of Efficacy and Integrated Summary of Safety
- A measurement report for the use of the HS Clinical Response (HiSCR)[2] measure
- 2 Evidentiary Dossiers to Support the use of various quality of life measurements in HS patients
- Literature references.

Paediatric data

The submission did not include paediatric data.

[2] HiSCR (Hidradenitis Suppurativa Clinical Response): At least a 50% reduction in the total abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count at a given clinical endpoint relative to Baseline. Measurement Report to Support the Use of the Hidradenitis Suppurativa Clinical Response (HiSCR) Measure to Assess the Impact of Adalimumab Treatment on Skin Lesions in Patients with Moderate to Severe Hidradenitis Suppurativa. October 2014 Abbvie Inc.

Comment: The exclusion of paediatric patients is reasonable given the low incidence of HS in prepubertal children and lack of evidence for the use of adalimumab in adolescent HS patients.

Good clinical practice

The sponsor declared that all individual studies in this application complied with the principles of Good Clinical Practice, and were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was reported to have occurred for all subjects, and the studies performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted.

Comment: No evidence was found by the evaluators to contradict this claim.

Pharmacokinetics (PK)

Studies providing pharmacokinetic data

Summaries of the pharmacokinetic studies are presented in Table 4.

Comment: Adalimumab is a registered drug for various indications in Australia. Pharmacokinetic data are available in the approved PI. No separate pharmacokinetic studies were submitted in this application. Rather, the presented data were derived as part of the pivotal efficacy/safety studies. Population pharmacokinetics was also evaluated for HS subjects in this submission.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in special populations	Target population (HS) § Multi–dose	M10–467 M11–313 M11–810
Population PK analyses	Healthy subjects	–
	Target population	M10–467 M11–313 M11–810
	Other	–

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

Evaluator's conclusions on pharmacokinetics

Adalimumab is a registered drug for several inflammatory conditions in Australia. The PK data of adalimumab in normal human subjects and approved indications were provided in previous submissions by the sponsor. Key PK data from these studies have been included in the PI sheet. The evaluation is based on PK obtained during submitted pivotal efficacy/safety studies in HS patients. The submitted data together with historical data on

other patient groups (that is UC and CD which have similar dosing regimens as HS patients) are acceptable for judging the PK in the HS population group.

Long term treatment serum concentrations of adalimumab in the three pivotal HS studies were largely consistent and were around 9 to 11 μg/mL for 40 mg every week (qw) at Week 36. Slightly higher trough concentrations were observed in Period A[3] in Study M10-467as compared to Studies M11–313 and M11–810, but this may relate to the different sample sizes and patient groups in the Phase II versus Phase III studies.

Compared to other study populations, including CD and UC, HS populations appeared to have lower adalimumab serum levels despite similar dosing. This may relate to the fact that HS patient groups have different demographics as compared to the other patient groups.

An inconsistency between presented PK in psoriatic patients in the submission and the PI needs to be clarified (that is, the PI states that trough concentrations were 5 μg/mL during adalimumab 40 mg fortnightly monotherapy, which is lower than the trough concentration observed in HS patients).

Serum adalimumab concentration was a significant predictor for loss of response (LOR)[4] in subjects who achieved HiSCR[2] at Week 12 and for worsening of underlying HS where subjects with higher adalimumab concentrations were less likely to experience LOR or HS worsening. LOR in subjects who achieved HiSCR at Week 12, and rates of flares and HS worsening were related to lower adalimumab concentrations, as observed in Period B.

Regarding immunogenicity, the percentage of subjects testing positive for anti-adalimumab antibody (AAA) who received 40 mg qw through Week 36 was 10%. Development of AAA may be associated with lower adalimumab serum concentrations and, therefore, may impact on the efficacy of therapy. There was no increased risk of any adverse event (AE) in AAA+ as compared to AAA- subjects, although sample numbers were low and further studies are required for definitive conclusions about AAA and safety.

Overall, the PK data provided in the submission are consistent with previous data in other patient groups. The proposed PI is generally an adequate summary of the PK presented in the submission.

Pharmacodynamics

Studies providing pharmacodynamic data

No pharmacodynamic data were provided.

Dosage selection for the pivotal studies

The dosing regimens for the pivotal studies (M11–810, M11–313) were selected based on data from Study M10–467, a 52–week 2–period Phase II study. The proportion of HS subjects who achieved a clinical response in Study M10–467 was significantly higher in

[3] Clinical efficacy studies with adalimumab in HS looked for evidence about short term induction therapy in 'Period A' for up to 12 weeks (Week 0-Week 12); after 'Period A' subjects entered 'Period B' where studies looked for evidence about maintenance treatment for an additional 24 weeks (Week 12-Week 36). Beyond 36 weeks subjects could enter into an Open Label Extension study. Adalimumab 2.5 Clinical Overview R&D/13/738

[4] LOR (loss of response): A loss of at least 50% of the improvement (reduction) in the AN count achieved from Baseline to Week 12. A phase III Open Label Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Hidradenitis Suppurativa PIONEER (Open Label Extension) AbbVie Inc. (Abbvie). Clinical Study Report (Interim) R&D/13/1034 Adalimumab/Protocol M12-555

the adalimumab 40 mg qw arm and numerically higher in the adalimumab 40 mg every other week (q2w) arm compared with subjects in the placebo arm at Week 12 and Week 16. A numerical trend favouring adalimumab 40 mg qw compared with adalimumab 40 mg q2w was noted at both Week 12 and Week 16. A decline in response rate was seen following the decrease from adalimumab qw to q2w dosing during Period B; dose escalation to adalimumab qw dosing resulted in improved efficacy.

Efficacy

Studies providing efficacy data

The sponsor provided three pivotal efficacy studies (M11–313, M11–810, M12–555) for the HS indication.

Comment: While Studies M11–313 and M11–810 are acceptable as pivotal efficacy studies, M12–555 represents an open label extension study of these two Phase III trials. At the time of submission, this study was still ongoing and was therefore not considered pivotal by the evaluator.

Evaluator's conclusions on efficacy

Study M10–467 represented the basis for the selection of adalimumab qw in Period A in the pivotal efficacy studies. This was appropriate as adalimumab qw population and placebo population had a statistically significant difference in HiSCR**Error! Bookmark not defined.** rate, compared to adalimumab q2w population versus placebo population. The choice of adalimumab qw dosing for the subsequent studies and also the proposed PI is acceptable. The overall HiSCR rates in both placebo and treatment groups were lower in all groups in Study M10-467, as compared to M11–313 and M11–810. The reason for this discrepancy is unclear and should be addressed by the sponsor.

The two pivotal efficacy studies, Study M11–313 and M11–810, were well designed and conducted. The double blinding methods were acceptable. The primary outcome of achieving HiSCR is a validated and clinically meaningful endpoint for assessing efficacy in moderate to severe HS. The two pivotal efficacy studies appear internally valid. The study population is adequately representative of the population likely to receive adalimumab for HS (more common in young women, high body mass index [BMI] and smokers). The inclusion and exclusion criteria were appropriate.

The primary end points were reached in both pivotal studies. A statistically significant proportion of subjects in the adalimumab qw group achieved HiSCR at Week 12 as compared to placebo in both Studies M11–313 and M11–810 (41.8% versus 26.0% $p = 0.003$, 58.9% versus 27.6% $p < 0.001$, respectively). The pooled analyses of the two studies, showed a statistically significant higher HiSCR rate in the adalimumab qw group compared to placebo at Week 12 (50.6% compared to 26.8%, $p < 0.001$). The difference was statistically significant in both Hurley Stage II and Hurley Stage III disease (Table 1); however the treatment effect was more prominent for Hurley Stage III. The difference of 23.9% in the pooled analysis is clinically meaningful at Week 12. It was unclear why the HiSCR rate in the placebo groups was high. This could relate to the inherently fluctuating disease course of HS, but the sponsor is encouraged to comment on this point.

In Study M11–313, all 3 ranked secondary endpoints did not achieve statistical significance. All 3 ranked secondary endpoints had very similar results in the adalimumab qw group and placebo group. In contrast, all 3 ranked secondary endpoints achieved statistical significance in Study M11–810 (all $p < 0.01$). The two populations in the different studies are similar, and the study design was identical in Period A. The difference in outcome is unexplained.

In contrast to short–term adalimumab therapy (3 months), the evidence for maintenance of effect is not convincing. In Period B of both pivotal studies, there was no significant difference in HiSCR and the Dermatology Life Quality Index (DLQI)[5] between adalimumab qw/qw, qw/q2w or qw/pbo for maintaining response in subjects considered responders at Week 12. There was approximately a 50% LOR[4] in both adalimumab qw and adalimumab q2w populations in Period B. The subgroups should be interpreted with caution as the numbers were low (< 30). There is limited evidence of clinically meaningful efficacy maintenance.

A separate analysis group of responders/partial responders was identified post hoc (ITT_B_PRR). This group analysis should be interpreted with caution. The selection criteria for this group seemed somewhat arbitrary and its clinical meaningfulness is questionable. The ITT_B_PRR population did demonstrate a statistically significant difference in HiSCR rate between qw/qw and qw/pbo population at Week 36 (55.7% versus 30.1%, $p < 0.05$), which was not seen between qw/q2w and qw/pbo population. The decreasing response rate even in the pooled responder/partial responder population is still concerning.

Overall, evidence for the short term benefits of adalimumab treatment of subjects with moderate to severe HS is convincing. However, there is limited evidence of a clinically meaningful maintenance of efficacy. Nevertheless, this needs to be considered in the context of the lack of HS treatment options. There has been no other randomised placebo controlled trials conducted that shows a significant clinical response in HS. HS is a debilitating condition with physical and psychological impacts. There are limited effective treatment options, and the only curative treatment is surgical excision and flap repair.

Safety

Studies providing safety data

Pivotal studies that assessed safety as a primary outcome:

- Studies M11–313 and M11–810 were pivotal studies that assessed safety as a primary outcome.

Dose response and non-pivotal efficacy studies:

- Study M10–467 provided data on safety, including treatment emergent adverse event (TEAEs) and laboratory variables (22 April, 2009 to 9 November 2010).
- Study M12–555 provided data on safety, including adverse events (AEs) and adverse events of special interest (AESIs) (12 April 2012 to 29 April, 2014).

Patient exposure

Across the studies, a total of 727 subjects with HS received at least 1 dose of adalimumab as of 29 April 2014 for a cumulative exposure of 635.7 patient years (PYs). Of these subjects, 576 subjects (79.2%) had been exposed to adalimumab for at least 6 months, 336 subjects (46.2%) had been exposed to adalimumab for at least 1 year, and 69 subjects (9.5%) had been exposed to adalimumab for over 2 years. The mean (standard deviation)

[5] DLQI (Dermatology Life Quality Index): an index used to assess the symptoms and the impact of skin problems on quality of life. The DLQI evaluates symptoms and feelings, daily activities, leisure, work and school, personal relationship, and treatment based on a recall period of the last week. The DLQI ranges from 0–30, with lower scores reflecting less impairment and improved health–related quality of life. (Finlay AY, Khan GK: *Dermatology Life Quality Index (DLQI) - a simple practical measure for routine clinical use.* Clin Exp Dermatol. 1994 May; 19(3):210-6.)

duration of adalimumab exposure was 319.4 (168.26) days and the median (minimum to maximum) duration was 321 (5 to 883) days.

Safety issues with the potential for major regulatory impact

The safety issues of most concern for adalimumab are serious infections and malignancies. The rates of TEAEs were similar to previous studies in approved adalimumab indications.

Post marketing data

Adalimumab was first approved for treatment of RA on 31 December 2002 (international birth date [IBD]). As of 31 December 2013, adalimumab has been evaluated in over 42,000 subjects (exposure of > 43,000 PYs) with RA, JIA, paediatric enthesitis related arthritis, PsA, CD, paediatric CD, Ps, paediatric Ps, UC, AS, spondyloarthritis (SpA), non–radiographic axial SpA (nr–axSpA), HS, uveitis, and intestinal Behçet's disease. Adalimumab is approved for the treatment of RA, AS, PsA, CD, Ps, UC, and JIA in the EU and US. The estimated cumulative post-marketing patient exposure since the IBD through 31 December 2013 is 2.9 million PYs.

The sponsor continues to monitor for potential new safety signals through its ongoing standard postmarketing safety surveillance practices for adalimumab. This surveillance includes reports of serious adverse events from clinical studies, all reports from spontaneous sources, the literature, regulatory agencies, post-marketing studies and registries. Eight AbbVie–sponsored adalimumab safety registries are ongoing with > 32,000 adult and paediatric patients. One Abbvie–sponsored clinical trial of 3,435 patients with moderate to severe RA (ReAlise) has been completed. New safety risks that are identified from the post-marketing experience are reflected in the company core labelling for the product. The post-marketing safety data with adalimumab in the approved adult indications has been consistent with the types and severity of AEs observed in the clinical trials for these patients HS.

Evaluator's conclusions on safety

In the two Phase III trials, the recommended adalimumab dose regimen for adult patients with moderate to severe HS was safe and well tolerated. Safety data were generated using appropriate methods. No new safety signals were identified in the HS program. The adalimumab treatment demonstrated higher rates of injection site reactions compared with placebo treatment. The two deaths in these studies did not appear to be related to adalimumab treatment. The observation period of 36 weeks in the Phase III trials does not allow evaluation of risks in the long–term.

In the open label study, no new safety risks for adalimumab were identified as of the 29 April 2014 data cut-off date. Adalimumab was generally well tolerated as evaluated by TEAEs, laboratory values, and vital signs values. One death was reported during the study in a subject who had multiple serious adverse events (SAEs) that included autoimmune pancreatitis, sepsis, cholangitis, and cardiac arrest. The death was considered unrelated to study drug by the investigator.

Overall, the incidence and severity of TEAEs, premature discontinuations due to TEAEs, and changes in laboratory and vital sign values were generally comparable between the adalimumab and placebo groups, as well as between the adalimumab qw and q2w groups, and were consistent with a population of subjects with moderate to severe HS. The rates of treatment emergent adverse event of special interest (AESI) were generally consistent with previous studies in approved adalimumab indications, such as Ps, UC or CD.

First round benefit–risk assessment

First round assessment of benefits

HS is a debilitating dermatological condition with very limited effective treatment options. Evaluation of the data contained in this proposal revealed the following benefits of adalimumab therapy in HS:

- In two pivotal studies, M11–313 and M11–810, short course (12 weeks) adalimumab treatment of HS produced meaningful clinical responses. Statistically significant proportions of subjects in the adalimumab qw group in both trials achieved HiSCR[2] (primary end point). These well conducted randomised controlled trials are the first to demonstrate a significant treatment option for HS.
- The selection of adalimumab qw dosing was evidence based, with adalimumab qw population and placebo population achieving significant difference in HiSCR rate, compared to adalimumab q2w population versus placebo population in the Phase II Study, M10–467.
- Short term adalimumab was effective as a treatment option for HS patients with Hurley Stage II and III disease (Table 1). The treatment effect was most prominent in subjects with severe Stage III disease.
- Short term adalimumab was effective in the typical HS population (young women, high BMI and smokers), who will be the most likely to receive the treatment.
- No clear evidence of a clinically meaningful maintenance of efficacy beyond 12 weeks of therapy. There was approximately a 50% LOR[4] in both adalimumab qw and adalimumab q2w populations in Period B[3].

First round assessment of risks

The risks of adalimumab in the proposed usage are:

- Overall, the incidence and severity of TEAEs, premature discontinuations due to TEAEs, and changes in laboratory and vital sign values were generally comparable between the adalimumab and placebo groups, as well as between the adalimumab qw and q2w groups, and were consistent with a population of subjects with moderate to severe HS.
- No new safety signals were identified.
- Adalimumab treatment consistently demonstrated higher rates of injection site reactions compared with placebo treatment.
- Ten percent of subjects receiving adalimumab developed AAA. The long term effect of adalimumab immunogenicity on its efficacy and safety profiles remains unknown.

The overall safety profile of adalimumab in the HS indication is consistent with other approved indications, such as CD, UC and Ps.

First round assessment of benefit–risk balance

The benefit–risk balance of adalimumab, given the proposed usage in HS, is favourable for short–term or induction treatment for 12 weeks.

First round recommendation regarding authorisation

A 12 week course (as per dosing protocol) of adalimumab provides a statistically significant and clinically meaningful treatment option in the management of HS. Pivotal studies were performed in patients with Hurley stage II or III disease (Table 1), and thus treatment should be limited to this subset of patients. The evidence does not demonstrate a significant benefit from ongoing maintenance treatment with adalimumab qw compared to placebo after this initial 12 week period. As such, the clinical evaluator recommends approval for 12 weeks of adalimumab as per dosing protocol (160 mg at week 0, 80 mg at Week 2, thence 40 mg every week from Week 4 to Week 12), but not for ongoing maintenance treatment.

Clinical questions

Efficacy

1. The overall HiSCR[2] rates in both placebo and treatment groups were lower in all groups in Study M10–467, as compared to M11–313 and M11–810. The reason for this discrepancy is unclear and should be addressed by the sponsor.
2. In Study M11–313 and M11–810 the HiSCR rate in the placebo groups were unusually high (26.0% and 27.6%). The sponsor is encouraged to comment on this point. Is this only related to inherently fluctuating disease or specific features of the study?

Second round evaluation of clinical data submitted in response to questions

Efficacy

Question 1

Sponsor`s response:

The HS–PGA (Table 2) was the primary efficacy endpoint for Study M10–467 and the HiSCR[2] was the primary efficacy endpoint for Studies M11–810 and M11–313. These endpoints have different definitions of clinical response and cannot be directly compared. To provide a more appropriate comparison of these data, post hoc analyses were performed on the dataset from Study M10–467 in which subjects with Hurley Stage I disease (Table 1) were excluded. This modified population of subjects was similar to the population studied in Studies M11–810 and M11–313. Of the subjects in this post hoc population, more subjects treated with adalimumab 40 mg qw achieved HiSCR than subjects treated with placebo at Week 12 (61.1% versus 16.2%, $p < 0.001$) and at Week 16 (55.6% versus 21.6%, $p = 0.003$) (Table 5).

These results are similar to what were observed in the Phase III studies at Week 12 (Study M11–810: 58.9% versus 27.6%, p = < 0.001; Study M11–313: 41.8% versus 26.0%, $p = 0.003$) (Table 6).

Table 5: Proportion of subjects achieving HiSCR[2] at Week 12 and Week 16 in Study M10–467 (non-responder imputation [NRI])[6] (mITT–1 population)

Visit	Placebo n/N (%)	Adalimumab ew n/N (%)	Difference, %	(95% CI)[a]	*P* Value[b]
Week 12	6/37 (16.2)	22/36 (61.1)	44.4	(21.9, 66.8)	< 0.001*
Week 16	8/37 (21.6)	20/36 (55.6)	32.2	(11.2, 53.2)	0.003*

ew = every week; CI = confidence interval; NRI = nonresponder imputation

a. 95% CI for strata-adjusted difference (Hurley Stages II versus III) based on CMH test corresponding to the extended Mantel-Haenszel statistic.

b. *P* value for pairwise comparison: ew versus placebo.

Note: Across overall strata, *P* values are calculated from the Cochran Mantel Haenszel test adjusted for strata.

* Denotes $P \leq 0.05$.

Table 6: Proportion of subjects achieving HiSCR[2] at Week 12 in Studies M11–810 and M11–313 (NRI)[6](ITT_A Population)

Study	Placebo n/N (%)	Adalimumab ew n/N (%)	Difference %	(95% CI)[a]	*P* Value[b]
M11-810	45/163 (27.6)	96/163 (58.9)	31.5	(20.7, 42.2)	< 0.001*
M11-313	40/154 (26.0)	64/153 (41.8)	15.9	(5.3, 26.5)	0.003*

CI = confidence interval; ew = every week; HiSCR = Hidradenitis suppurativa clinical response; NRI = nonresponder imputation

a. 95% CI for strata-adjusted difference (baseline Hurley Stage in M11-313, baseline Hurley Stage and antibiotic use for Study M11-810) was calculated according to the extended Mantel-Haenszel statistic for the comparison of 2 treatment groups.

b. *P* value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata.

Note: * Denotes $P \leq 0.05$.

Evaluator´s comment:

The response sufficiently addresses the clinical question and explains the initial apparent difference between the clinical response rates in M10-46, and 7 Studies M11-810 and M11-313.

Question 2

Sponsor´s response:

HS is a chronic, inflammatory skin condition known to have periods of quiescence and flare. Limited data on the natural history of the disease are available to fully characterise disease activity in HS and there are no published prospective studies of the clinical course of HS that can provide expected placebo response rates.

Studies M11–810 and M11–313 are the first large placebo–controlled Phase III studies that investigate a pharmaceutical intervention and were the first studies to prospectively use a newly validated measure, HiSCR, as the primary efficacy endpoint. HiSCR is defined as at least a 50% reduction in the total abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to Baseline. As with any placebo–controlled clinical trial, it is expected that some subjects in the placebo group will have a response. Given the fluctuations in the course of HS and considering the definition of achieving HiSCR, some response to placebo would be expected in the study population.

[6] NRI (Non-responder imputation): A standard statistical strategy for handling missing data: any subject who drops out is assumed to be a non-responder.

A subgroup analysis of the integrated data from Studies M11–810 and M11–313 by baseline AN count category (≤ 5, 6 – 10, and > 10) showed the response to placebo varied, depending on the baseline AN count (Table 7). Specifically, the HiSCR rate decreases as the baseline AN count increases, reflecting a greater threshold to achieve at least a 50% decrease in the AN count without adalimumab intervention. In contrast, HiSCR rates for the adalimumab group were similar across the 3 categories; the treatment difference was greatest in the baseline AN count category of > 10. Despite the observed placebo response in both Phase III studies, the percentage of subjects in the adalimumab group who achieved HiSCR at Week 12 was significantly higher than subjects in the placebo group. These results represent a clinically meaningful difference between treatment groups.

Table 7: Number and proportion of subjects who achieved HiSCR[2] at Week 12 by baseline AN count (NRI)[6](ITT_A Population)

	Subjects, n/N (%)			
Lesion Subgroup	Adalimumab ew	Placebo	Difference, %	*P* value
AN count ≤ 5	39/71 (54.9)	30/86 (34.9)	20.5	0.011
AN count 6 – 10	56/115 (48.7)	26/84 (31.0)	18.8	0.008
AN count ≥ 11	65/130 (50.0)	29/147 (19.7)	30.1	< 0.001

Strata-adjusted differences were reported.

'Adalimumab ew' in Tables 5-7 stands for adalimumab every week (qw) treatment.

Evaluator´s comment:

The response is acceptable. The fluctuating clinical nature of HS is likely to explain the high HiSCR rates in the placebo groups. The sponsor shows that the HiSCR rates decrease in the placebo groups with a higher baseline AN count. Despite the high HiSCR rates in the placebo groups, there was a statistically significant higher HiSCR rate at Week 12 in the adalimumab ew group compared to the placebo group (50.6% compared to 26.8%, $p < 0.001$).

Second round benefit–risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of adalimumb in HS patients in short–term usage (12 weeks) are unchanged. For maintenance therapy after 12 weeks, the sponsor provides acceptable arguments for the benefits of adalimumab, including post hoc analysis of patient groups. While this is circumstantial evidence, the clinical evaluator has taken this clinical experience into consideration. Together, the use of adalimumab for the treatment of HS beyond 12 weeks is considered appropriate if assessment of the HiSCR[2] response shows at least 50% improvement. It is recommended to perform HiSCR assessments at 12 and 24 weeks, and 6 monthly intervals thereafter.

Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of adalimumab are unchanged from those identified in the First round evaluation.

Second round assessment of benefit–risk balance

The benefit–risk balance of adalimumab, given the proposed usage in HS, is favourable. The benefit–risk balance is unchanged from the initial proposal.

Second round recommendation regarding authorisation

A 12–week course (as per dosing protocol) of adalimumab provides a statistically significant and clinically meaningful treatment option in the management of HS. Pivotal studies were performed in patients with Hurley stage II or III disease (Table 1), and thus treatment should be limited to this subset of patients.

The large loss of response rates of 47.6% and 54.7% respectively in Study M11–313 and M11–810 are concerning. After consideration of the sponsor's response and revisiting the pivotal Studies M11–313 and M11–810, the evaluator acknowledges that the participants who lost response and entered into Study M12–555, was not given the opportunity to demonstrate any subsequent improvement and regain HiSCR. The pooled Period B[3] analysis from Study M11–813 and M11–810 demonstrates a statistically significant difference in HiSCR response between ew/ew and ew/pbo adalimumab dosing at Week 36 (43.4% and 28.0%, $p < 0.05$).

As such, the clinical evaluator recommends approval for 12 weeks of adalimumab as per dosing protocol (160 mg at week 0, 80 mg at Week 2, thence 40 mg every week from Week 4 to Week 12). The clinical evaluator recommends assessment of HiSCR response at Weeks 12 and 24. HiSCR responses should be assessed every 6 months thereafter. A positive HiSCR response should be present for continuation of treatment at the assessment timepoints. Patients, who demonstrate maintenance of HiSCR response, should be given ongoing maintenance treatment.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU–RMP 11.1.2 dated September 2014 with an Australian Specific Annex [ASA] Version: 2.0 dated December 2014) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 8.

Table 8: Summary of Safety Concerns

Summary of Safety Concerns	
Important Identified Risks	Serious infections including diverticulitis and opportunistic infections for example invasive fungal infections, parasitic infections, legionellosis and tuberculosis. Reactivation of hepatitis B Pancreatitis Lymphoma Hepatosplenic T–cell lymphoma (HSTCL) Leukaemia Non–melanoma skin cancer (NMSC) Melanoma

Summary of Safety Concerns	
	Merkel Cell Carcinoma Demyelinating disorders (including Multiple Sclerosis, Guillain Barré Syndrome and optic neuritis) Immune reactions (including lupus–like reactions and allergic reactions) Sarcoidosis Congestive Heart Failure Myocardial Infarction Cerebrovascular accident Interstitial lung disease Pulmonary embolism Cutaneous vasculitis Stevens–Johnson Syndrome and erythema multiforme Worsening and new onset of Psoriasis Haematologic disorders Intestinal perforation Intestinal strictures in Crohn's disease Liver failure and other liver events Elevated ALT levels Autoimmune hepatitis Medication errors and maladministration
Important Potential Risks	Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC and melanoma) Vasculitis (non–cutaneous) Progressive multifocal leukoencephalopathy Reversible posterior leukoencephalopathy syndrome Amyotrophic Lateral Sclerosis Colon cancer in Ulcerative Colitis patients Infections in infants exposed to adalimumab in utero Medication errors with paediatric vial Off–label use
Missing information	Subjects with immune–compromised conditions (i.e. subjects with HIV, post–chemotherapy, organ transplant); subjects with a history of clinically significant drug or alcohol abuse Subjects with poorly controlled medical conditions such as uncontrolled diabetes or documented history of recurrent infections, unstable ischaemic heart disease, congestive heart failure, recent

Summary of Safety Concerns	
	cerebrovascular accidents Subjects with a history of listeriosis, history of histoplasmosis, active tuberculosis, persistent chronic or active infections requiring treatment with antibiotics, antivirals or antifungals, history of viral hepatitis Subjects with a history of cancer, lymphoma, leukaemia or lymphoproliferative disease; subjects with history of neurologic symptoms suggestive of demyelinating disorders Children < 18 years of age for PsA, AS, Ps, UC, SpA, HS, enthesitis related arthritis, and uveitis indications Children < 2 years of age for JIA Children < 6 years of age for CD and enthesitis related arthritis. Pregnant and lactating women Subjects with renal or liver impairment Patients taking concomitant biologic therapy Long–term rheumatoid arthritis data beyond 10 years Long–term juvenile idiopathic arthritis data beyond 7.5 years Episodic treatment in juvenile idiopathic arthritis Long term ankylosing spondylitis data beyond 5 years Long term axial spondyloarthritis (SpA) data beyond 1 year Short and long term peripheral SpA data Remission–withdrawal–retreatment axial SpA data Short and long term paediatric enthesitis related arthritis (pedERA)data Long term PsA data beyond 3 years Long term Ps data beyond 6 years Episodic treatment in Ps Short and long term hidradenitis suppurativa data Long term CD data beyond 5 years Episodic treatment in CD Long term paediatric CD data beyond 2 years Long term UC data Episodic treatment in UC Short and long term uveitis data

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor proposes routine pharmacovigilance activities to monitor all the specified safety concerns and missing information.

The ASA states: '*AbbVie will continue to educate physicians about the appropriate use of adalimumab. If new important safety signals are detected through routine pharmacovigilance monitoring this will be reflected in the local approved product information. Any information that is received that may alter the content of the RMP will be updated and re–submitted to Therapeutic Goods Administration for review. The AbbVie pharmacovigilance system will continue to monitor adalimumab on the market and guarantee that appropriate actions are taken when necessary*'.

Additional pharmacovigilance activities are also proposed to further monitor and characterise the following:

- the important identified risks: 'Serious infections including diverticulitis and opportunistic infections e.g. invasive fungal infections, parasitic infections, legionellosis and tuberculosis', 'Merkel Cell Carcinoma', 'Elevated ALT levels' & 'Autoimmune hepatitis';
- the important potential risk: 'Colon cancer in UC patients'; and
- the missing information relating to safety information in the treatment of children < 18 years of age for Ps, UC, nr-axSpA and children < 6 years of age for pedCD and long term safety information in the treatment of children aged 6 years to < 18 years with pediatric enthesitis related arthritis (pedERA), pregnant and lactating women, and remission-withdrawal retreatment nr-axSpA data and episodic treatment in Ps, CD, UC, and JIA.

The ASA states: *'An overview of the ongoing and planned studies is summarized in Table 3' [not in this AusPar]*.

There are no observed changes to the pharmacovigilance plan previously accepted for Humira (adalimumab (rch)).

Reconciliation of issues outlined in the RMP report

Table 9 summarises recommendation of the RMP evaluation report and the sponsor's responses to issues raised.

Table 9: Reconciliation issues outlined in the RMP Evaluation Report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
It is drawn to the Delegate's attention that the foreshadowed new indication in the EU positions Humira as a second line therapy for the treatment of active moderate to severe HS in adult patients, rather than as first line therapy as sought for in Australia. The sponsor should amend Table 2a: 'Adalimumab Registrations Under Evaluation or Under Development in the European Union and Australia' of the ASA to explain the reasons for this difference.	The sponsor states: '*AbbVie's position for use of adalimumab in the treatment of HS is as a first line therapy because there is currently a lack of approved therapy for HS*' and '*as requested, AbbVie has amended Table 2a of the revised ASA (version 5.0), Adalimumab Registrations Under Evaluation or Under Development in the European Union and Australia, to reflect the indication in Australia and the EU*'.	The former response is for the Delegate's consideration, while the latter is acceptable.
The sponsor should update Table 1: 'Adalimumab Formulations Registered in Australia' and Table 2: 'Adalimumab Registrations in the European Union and Australia' (as it relates to polyarticular juvenile idiopathic arthritis) of the ASA.	The sponsor states: '*AbbVie has updated Table 1 and Table 2 of the revised ASA (version 5.0)*'.	This is acceptable.
Safety considerations may be raised by the clinical evaluator through the TGA consolidated request. It is important to ensure that the information provided in response to these include a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor states: '*AbbVie acknowledges that issues raised throughout the clinical evaluation process may impact the Humira RMP and an assurance is provided that the RMP will be revised to include relevant information needed to address new safety considerations*'.	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
For the missing information related to safety information in the treatment of children < 6 years of age for pedCD, and long term safety information in the treatment of children aged 6 years to < 18 years with pedERA', Table 3: 'Overview of Ongoing and Planned Pharmacovigilance Actions' of the ASA should be amended to include details of Study M11-328 to be consistent with Table 100: 'Required Additional Pharmacovigilance Activities' of the EU–RMP.	The sponsor states: "AbbVie would like to point out that this information has been captured in version 4.0 of the ASA, which was submitted recently in PM–2015–01149–1–3. Please refer to Table 3, Overview of Ongoing and Planned Pharmacovigilance Actions, on page 46 (of 79)".	This is acceptable.
For clarity and as per the ASA template, as found on the TGA website as of 4 May 2015, the sponsor should include a table briefly summarising the pharmacovigilance and risk minimisation activities proposed for Australia in a revised ASA.	The sponsor states: '*AbbVie would like to point out that this information has been captured in version 4.0 of the ASA, which was submitted recently in PM–2015–01149–1–3. Please refer to Table 5, Summary of the Risk Minimisation Plan in Australia, on pages 58 –68 (of 79)*'.	In the first instance Table 5 should be renamed and corrected to 'Summary of the Risk Management Plan in Australia'. Secondly it is apparent that the specified missing information in Table 4: 'Summary of the Risk Minimisation Plan in Australia' and Table 5 of the updated ASA has been significantly rationalised, including the deletion of 'Subjects with renal or liver impairment', compared to what was previously accepted for Humira. It would appear the only justification offered for such change was 'Missing information was updated', which is considered to be inadequate. Consequently the sponsor should provide compelling justification for apparent changes to the missing information items previously accepted for Humira or alternatively reinstate these safety concerns, which need only be reflected in a revised ASA preferably before this application is approved.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

At this time no wording can be provided, as it is recommended that an acceptably revised ASA be submitted before this application is approved.

Summary of recommendations

See second round RMP report.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

HS is a chronic follicular occlusive disease involving the follicular portion of folliculo-pilo-sebaceous units[1]. Primary sites are intertriginous skin areas of the axillary, groin, perianal, perineal and inframammary regions. Clinical manifestations range from recurrent inflamed nodules and abscesses through to draining sinus tracts and bands of severe scarring. Pain, malodour, drainage and disfigurement contribute to a profound psychosocial impact. Onset is usually between puberty and 40 years. Incidence is higher in women. There is a strong correlation with smoking, and a weaker correlation with obesity.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a quality evaluation in a submission of this type.

Clinical

There were two pivotal studies (M11–313 and M11–810), with similar design (including use of a newly validated endpoint, HiSCR**Error! Bookmark not defined.**). These studies examined efficacy in 'Period A' up to week 12, when HiSCR was assessed. After week 12, patients entered 'Period B' for 24 weeks and generated evidence about maintenance treatment. Beyond Week 36, some evidence has been generated in the open label extension study M12–555.

The clinical evaluator considered that a 12 week course of adalimumab was beneficial in management of HS, but did not initially consider there to be a significant benefit from ongoing 'maintenance' treatment. The final recommendation took into account further

justification from the sponsor, and was to allow maintenance use. However, the clinical evaluator's view is that only with ongoing evidence of efficacy should maintenance continue.

- The clinical evaluator recommends assessment of HiSCR response at Weeks 12 and 24. HiSCR responses should be assessed every 6 months thereafter. A positive HiSCR response should be present for continuation of treatment at the assessment timepoints. Patients, who demonstrate maintenance of HiSCR response, should be given ongoing maintenance treatment.

The implication is that only responders at Week 12 should continue treatment (and so on, with re–assessment at Week 24 and every 6 months thereafter).

Pharmacokinetics (PK)

PK and immunogenicity were evaluated in patients enrolled in the two Phase III studies (M11–313 and M11–810) and the Phase II study (M10–467).

A key finding was that:

- At the end of Period A (Week 12), subjects were evaluated for the primary efficacy endpoint of HiSCR. In subjects that received adalimumab 40 mg ew, responders had slightly higher adalimumab concentrations compared to non-responders (8 to 11 µg/mL versus 6 to 7 µg/mL) in both Phase III studies.

There was some suggestion that with like dosing, exposure was lower in HS than in other disease states such as CD, UC and Ps, however this was not conclusively demonstrated, and no explanation was apparent for such a difference.

Another significant finding was that AAAs helped explain variability in apparent clearance.

In exposure–response analysis:

- Serum adalimumab concentration was a significant predictor for LOR[4] in *subjects who achieved HiSCR* and for HS reported as an AE (exacerbation of underlying disease). Subjects with higher adalimumab concentrations were less likely to experience LOR or HS as an AE.

In the Phase III studies around 10% of HS patients developed AAAs over periods ranging up to one year. From the small number of antibody positive patients (n = 10), no one achieved HiSCR at week 12. Numbers were too small to allow conclusions about correlation with safety.

Pharmacodynamics (PD)

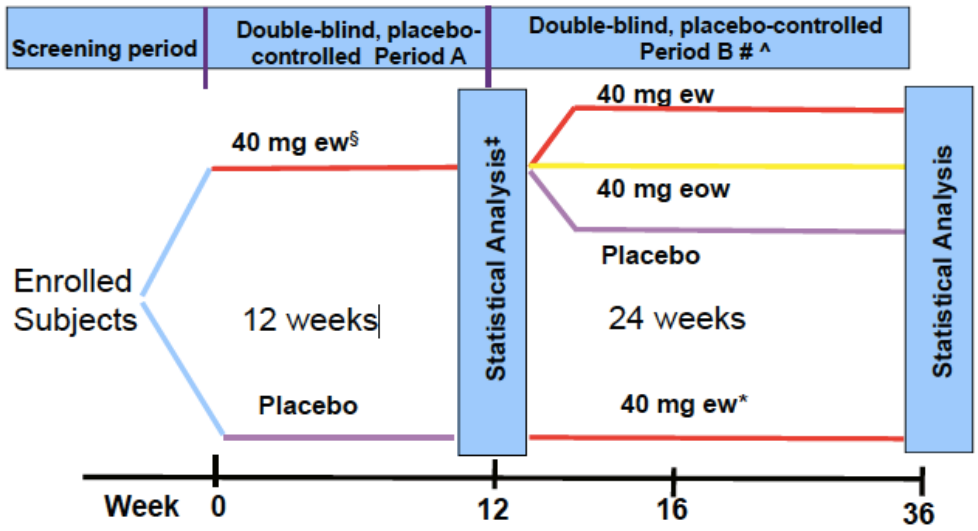
No data were submitted.

Efficacy

Study M11–313

This was a randomised, double–blind study of adalimumab versus placebo conducted across 48 centres globally, from 2011 to2014. Period A was the initial 12 week treatment phase; Period B was a 24 week treatment phase. Study design is best described by diagram (Figure 1).

Figure 1: Study M11-313



Adults with HR in at least two anatomic areas, one of which had at least Hurley Stage II disease (Table 1), and who had failed a 90 day trial of oral antibiotics, were eligible.

The primary endpoint was:

- the proportion of subjects achieving HiSCR[2] at Week 12.

The clinical evaluator thought this endpoint validated and meaningful.

Some 307 patients were randomised (n = 154 to placebo, n = 153 to adalimumab). There was a moderate disparity in gender distribution (68% female for placebo, 60% for adalimumab), age < 40 years (58% versus 67% respectively) and BMI (median 33.6 versus 32.1 respectively).

HiSCR at Week 12 was achieved in 26.0% (placebo) versus 41.8% (adalimumab). Broadly, this difference was maintained across subgroups.

There was no difference in several important secondary endpoints, across arms. However, quality of life was better in the adalimumab arm.

In Period B, randomisation tested whether an q2w regimen or even no further treatment provided better outcomes than ongoing ew treatment. Retention of Week 12 response was similar in the randomised qw and q2w arms, to Week 36, but not statistically significantly better than in the placebo arm. Dermatology quality of life indices were similar in the three arms. Results were based on small sample sizes. Conversion to response amongst Week 12 non-responders was seen in 37% for qw/qw, but 26% for qw/placebo. The clinical evaluator writes: *'continuation of adalimumab had no benefit over placebo for subjects who were classified as non-responders at Week 12'*.

Study M11–810

This study had a similar design to Study M11–313. It was conducted at 53 sites globally from 2011 to 2014. Key inclusion and exclusion criteria were as per Study M11–313. Dose regime was as per Study M11-313, except that patients initially randomised to placebo (that is in Period A[3]) were kept on placebo in Period B. The primary endpoint was as per Study M11–313.

Some 163 patients were randomised to placebo, and 163 to adalimumab (in Period A). There were some baseline imbalances, for example race, weight.

Some 58.9% of adalimumab qw patients versus 27.6% of placebo arm patients attained HiSCR[2] at week 12. This difference was maintained across subgroups. Secondary efficacy

endpoints were also in favour of adalimumab, which was not consistently the case in Study M11–313.

In Period B, in responders re–randomised to qw, q2w or placebo, retention of response was similar across qw and q2w adalimumab arms at 44 to 45% and only marginally better than in the Phase B placebo arm, at 35.5%. There was also little difference across the three arms (in the Week 12 responder population) in the DLQIs[5]. The evaluator concluded that there was no significant difference in HiSCR or DLQI across the three groups (in the Week 12 responder cohort) and that continuation of adalimumab beyond Week 12 has no benefit over placebo for Week 12 responders (based on these study results). In Week 12 non-responders, qw/qw patients did better, although no statistical analysis was provided.

Study M10–467

This Phase II study of adalimumab in HS patients provided a basis for the dose regimen used in the Phase III studies, in that 40 mg qw produced better results than 40 mg q2w. The clinical evaluator notes a lower response rate in this study than in the two Phase III studies, although in response to a question about this, the sponsor noted that primary endpoints and study populations differed from the Phase II to the Phase III studies.

Study M12–555

This was an open label extension study for subjects participating in Studies M 11–313 and M11–810. Inclusion criteria included:

- Subjects who participated in a prior Phase III study (Studies M11–810 or M11–313) and:
- Completed the study; or
- Achieved HiSCR[2] at the entry of Period B, then experienced LOR defined as an abscess + nodule count that was greater than the average of AN counts at Baseline and Week 12 of the prior Phase III study; or
- Did not achieve HiSCR at the entry of Period B, then experienced Worsening or Absence of Improvement on or after Week 16 of the prior Phase III study, defined as an AN count ≥ Baseline AN count at 2 consecutive visits (excluding Week 12) occurring ≥ 14 days apart.

All subjects received adalimumab 40 mg qw. Given the design of the M11-313, M11-810 and M12-555 Studies, there were multiple populations under study (for example qw/qw/qw versus qw/q2w/qw, and so on). As of 29 April 2014, n = 497 subjects had been analysed. At Week 72, the rate of subjects achieving HiSCR was highest in the qw/q2w/qw arm, at 62%; although the qw/qw/qw patients had a similar response rate, at 58%. The clinical evaluator considered results descriptive, and that efficacy conclusions should not be drawn from these population.

Pooled analysis

With the pre-specified pooled Period B[3] analysis, there was a statistically significant improvement in the rate of retention of response in the qw/qw arm versus the qw/placebo arm (43.4% at Week 36 for qw/qw, versus 28% for qw/placebo).

Safety

Safety of adalimumab in HS was examined in the four studies referenced above. Key are the placebo-controlled analysis set (n = 785) for short term safety, and the maintenance analysis set (n = 300) to Week 36 for slightly longer term safety. Across studies, n = 336 were exposed to adalimumab for ≥ 1 year, and n = 69 were exposed for ≥ 2 years.

Comment: Some of the 'treatment emergent' AEs may be considered to be 'treatment related'. A prominent finding in Period A was that treatment emergent AEs were less frequent in patients given qw adalimumab than in patients on placebo, and the finding extended to analysis of incidence rates. This was also so for major classes of AEs such as SAEs or AEs leading to discontinuation. Only for serious infection was frequency higher on adalimumab than on placebo, based on few events (2 amongst n = 366 for placebo, 3 amongst n = 367 for qw adalimumab).

In the Period B ('maintenance') set, again, there was no indication that adalimumab was linked more to AEs than with placebo. However it is assumed that AEs analysed during Period B had their onset essentially in Period A. These results are supported by the overall safety data in the document 'Integrated Summary of Safety R&D/13/1033)\'[7]. In this summary certain major types of AEs were seen more often in qw/qw patients than in qw/placebo patients, for example TEAEs (14.1 events / 100 PY versus 6.3 events / 100 PY, respectively).

To some extent, this picture of 'safety' is distorted by efficacy of adalimumab in treating HS, since hidradenitis was commonly reported as an AE. In examining common AEs, no major imbalances were observed between placebo and the two adalimumab groups (qw, q2w).

In discussion of the subject in M12–555 who died due to complications of pancreatitis, it is notable that the adalimumab PI mentioned pancreatitis as an uncommon adverse drug reaction.

Analysis of laboratory findings revealed no remarkable sign of toxicity for adalimumab, but triglyceride elevation was more common with adalimumab at 2.3% (versus 0% for placebo), which might be relevant given other cardiac risk factors in the HS population (that is overweight and smoking history). To a lesser extent, cholesterol was also elevated versus placebo (0.9% versus 0.3%). One 35 year old male in the Study M11–810 qw/q2w arm did indeed have a myocardial infarction on day 196 (and died on day 234), risk factors included diabetes mellitus and a 16 year history of heavy smoking, as well as a family history of early onset coronary heart disease.

The clinical evaluator notes that the observation period of 36 weeks in the Phase III trials *'does not allow evaluation of risks in the long–term'*.

Risk management plan

The RMP Evaluator has requested that the ASA to the EU–RMP be revised to summarise pharmacovigilance and risk minimisation activities proposed for Australia. The Delegate agrees that the sponsor should justify apparent significant changes, for example the deletion of reference to subjects with renal or liver impairment. The sponsor is asked to resolve this issue to the satisfaction of the TGA's RMP Evaluation area. This can proceed in parallel with a decision about the HS application.

The Delegate proposes to include the following RMP specific condition of registration:

> Implement EU–RMP Version 11.3.1, dated June 2015, with ASA Version 5.0, dated September 2015, and any updates accepted by the TGA's RMP Evaluation section.

[7] RD131033 Integrated Summary of Safety Text– Hidradenitis Suppurativa: A summary of all reported AE`s in the adalimumab clinical trials in hidradenitis suppurativa, a document submitted to TGA.

Risk-benefit analysis

Delegate's considerations

Issues

Efficacy in maintenance

The clinical evaluator considers that there is convincing evidence of a benefit for short term adalimumab therapy (supported by Week 12 HiSCR[2] outcomes in Studies M11–313 and M11–810, but does not consider the evidence for maintenance therapy to be convincing. In particular, the clinical evaluator noted a substantial LOR[4] despite either qw or q2w maintenance. The clinical evaluator also notes the lack of HS treatment options.

The following table (Table 10) is relevant from extension study M12–555:

Table10: Proportion of subjects achieving HiSCR[2] during study M12–555 (last observation carried forward [LOCF[8]]): qw/qw/qw, qw/q2w/qw, and qw/pbo/qew populations

Visit in Study M12-555[a]	EW/EW/EW N = 84 n (%)	EW/EOW/EW N = 90 n (%)	EW/PBO/EW N = 91 n (%)
Week 0× (Entry to Study M12-555)	43 (51.2)	33 (36.7)	28 (30.8)
Week 4×	46 (56.8)	36 (42.9)	41 (48.8)
Week 8×	46 (56.1)	44 (51.8)	43 (51.2)
Week 12×	45 (54.9)	43 (50.6)	47 (56.0)
Week 24×	45 (54.9)	50 (58.8)	48 (57.1)
Week 36×[b]	49 (59.8)	53 (62.4)	41 (48.8)
Week 48×[b]	47 (57.3)	52 (61.2)	44 (52.4)

EOW = every other week; EW = every week; HiSCR = hidradenitis suppurativa clinical response; LOCF = last observation carried forward; PBO = placebo

a. "×" refers to weeks relative to first dose in Study M12-555.

b. The number of observations at Weeks 36 and 48 are 40 and 22 for the EW/EW/EW group, 43 and 23 for the EW/EOW/EW group, and 39 and 20 for the EW/PBO/EW group.

Note: The data cutoff date was 29 April 2014. Results after Week 48 (from start of Study M12-555) are available for fewer than 20% of subjects.

'Adalimumab ew' in Tables 11-12 stands for adalimumab every week (qw), 'adalimumab eow' treatment stands for adalimumab every other week (q2w) treatment.

From this, it appears that in the qw/qw/qw cohort, few patients other than those who were already responders at extension study entry actually attained a response. Other cohorts (qw/q2w/qw, qw/pbo/ew) are less relevant as they do not conform with the PI-proposed dose regimen.

This and similar tables using other efficacy endpoints support the clinical evaluator's notion that maintenance is only justified if there is (ongoing) evidence of efficacy. There is no strong signal that non-responders will gain significant benefit with further weeks or months of therapy.

Comment: The sponsor includes a letter from a local expert regarding adalimumab in HS, which states in part: '*Adalimumab has been the first– and so far the only–therapy to enter Phase III studies in patients with moderate–to–severe HS. The expert recommendations recently presented at the 23rd World Congress of*

[8] LOCF (Last observation carried forward): A standard strategy for addressing the problem of missing data. It handles missing data by assigning the value recorded at the patient`s last visit to all subsequent missed visits.

> *Dermatology support the use of adalimumab after antibiotics have failed (level of evidence [9]1[b], strength of recommendation [10]A[2])[11]*'.

As per the extract, the view is that maintenance applies '*if improvement occurs*'.

The TGA evaluator's proposal is to ensure ongoing use is in those with ≥ 50% reduction from baseline in total abscess and inflammatory nodule (AN) count, with no observed increase in either abscess or draining fistula counts, at Week 12, Week 24 and every 6 months thereafter. This provides a concrete way to measure benefit and is an extension of the advice of the Summary of Product Characteristics (SmPC) that ongoing use be in patients showing improvement on therapy.

In the latest version of the proposed PI, the Dosage and Administration section includes text as follows: '*In patients without any benefit after 12 weeks of treatment, continued therapy should be reconsidered.*' The clinical evaluator's text provides more concrete advice in that it specifies how 'benefit' should be measured (HiSCR)[2] and when it should be measured (12 weeks, 24 weeks, then every 6 months), and requires that for ongoing use there should be maintenance of HiSCR. The Delegate supports the clinical evaluator's proposal. The ACPM's advice has been asked about this issue.

Indication

The proposed indication differs from the EU and US indications in specifying 'treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas'. This wording reflects the definition of the newly validated HiSCR endpoint and its use in the indication is acceptable, though perhaps not strictly necessary.

The EU indication requires inadequate response to conventional systemic therapy. The TGA clinical evaluator did not consider this necessary in the wording of the indication. The Clinical Trials section notes that patients studied in pivotal trials were intolerant, had a contraindication or an inadequate response to systemic antibiotic therapy. There is a suggestion to provide more detail about this (that is to note that trial of antibiotics was for 3 months). With this information provided in the PI, the wording of the indication is acceptable. The ACPM's advice has been asked about this issue.

Conclusion

The Delegate stated there is evidence of benefit, using the newly validated efficacy endpoint, HiSCR[2], after a 12 week course of therapy. In non-responders at Week 12, there is no adequate evidence that ongoing use is beneficial. In responders, there is evidence that benefit may be maintained with ongoing weekly treatment, in a reasonable proportion of patients. Evidence of ongoing efficacy is strongest to Week 36; an extension study is gathering evidence beyond this timepoint.

A key issue is what level of detail should be provided in the PI for advice about 'maintenance'. The sponsor proposes a statement that '*In patients without any benefit after 12 weeks of treatment, continued therapy should be reconsidered*'. The TGA Evaluator recommends more specific advice.

Another issue is that in the EU, this use of adalimumab has been restricted to second line after trial of antibiotics (where possible). In this submission, this is not built into the proposed indication. However, it is noted in the PI's Clinical Trials section that patients

[9] Level of evidence: A ranking system commonly used to describe the strength of the results measured in a clinical trial or a research study, using a scale from 1 to 5 being 1 the highest evidence.
[10] Strength of recommendation: A ranking system commonly used to describe the risk versus benefit at the given level of evidence using a scale from A to I being A the highest benefit/risk ratio.
[11] Gulliver W et al: Evidence–based approach to the treatment hidradenitis suppurativa/acne inversa based on the European guidelines for hidradenitis suppurativa. Presented at:23rd World Congress of Dermatology;June 8–13,2015; Vancouver, Canada. Abstract 3078692.

enrolled in the pivotal studies had in fact failed or could not use antibiotics. It should be noted that antibiotics are not formally indicated for this use by the TGA.

Proposed action

The application to extend adalimumab's indications to include a subset of patients with HS is acceptable. Several details (the exact wording of the indication; advice about maintenance use) require the advice of the Advisory Committee on Prescription Medicines (ACPM).

Proposed conditions of registration

- Implementation of the RMP version most recently approved by the TGA's Pharmacovigilance & Special Access Branch.
- Finalisation of the Product Information to the satisfaction of the TGA.

Proposed PI and Consumer Medicine Information (CMI) amendments to the:

- Clinical trials
- Adverse effects and
- Dosage and administration sections.

Request for ACPM advice

The Delegate requested advice on the following specific issues:

1. Should the PI include specific advice about how and when to measure ongoing treatment benefit, and should ongoing use be contingent on evidence of benefit measured in this way?
2. Is the sponsor's proposed indication wording acceptable, or should the indication specifically reference failure of a trial of systemic antibiotics (or inability to use antibiotics), as per the EU SmPC (but not the US PI)?

The Delegate also requested advice on any issues that the ACPM thinks may be relevant to a decision on whether or not to approve this application, including the proposed changes to the PI and CMI; the requirements for an acceptable RMP, the clinical significance and likely place of the product in clinical practice and the comments from the sponsor in the pre–ACPM response.

Response from sponsor

AbbVie Pty Ltd would like to take this opportunity to respond to the TGA review of the application to register Humira (adalimumab) solution for injection for the indication of HS.

Question 1

Should the PI include specific advice about how and when to measure ongoing treatment benefit, and should ongoing use be contingent on evidence of benefit measured in this way?

Sponsor's response:

AbbVie supports providing advice to clinicians regarding which patients are most likely to benefit from continued treatment with adalimumab. The complex and variable clinical manifestations of HS, however, make it impractical to define rigid criteria to identify which patients would benefit from continued treatment with adalimumab. The PI should provide guidance, but continuation of treatment is a clinical decision made by the prescribing physician and is based on an assessment of benefit–risk for an individual patient.

There is evidence that not only patients with HS who achieve HiSCR after 12 weeks of treatment, but also those who are partial responders (that is, those who had at least a 25% reduction in abscess and inflammatory nodule [AN] count) after 12 weeks of treatment, may benefit from continued treatment (Table 11). AbbVie recommends advising clinicians that continuation of treatment is appropriate in patients who have at least a partial response to initial treatment. Patients who do not have at least a partial response by Week 12 are unlikely to achieve HiSCR response with continued adalimumab treatment.

Table 11: Proportion of subjects who achieved HiSCR[2] at week 36 by AN25 status at entry to period B (NRI)(ITT_B_NR population, integrated analysis)

	AN25 Responder at Entry to Period B[a] n (%)			AN25 Nonresponder at Entry to Period B[a] n (%)		
Visit	ew/pbo (N = 20)	ew/eow (N = 18)	ew/ew (N = 18)	ew/pbo (N = 27)	ew/eow (N = 31)	ew/ew (N = 29)
Week 36	5 (25.0)	4 (22.2)	14 (77.8)[b,c*]	6 (22.2)	3 (9.7)	4 (13.8)

AN = abscess and inflammatory nodules; eow = every other week; ew = every week; NRI = nonresponder imputation; pbo = placebo

a. For between treatment group comparisons, *P* value calculated from the Cochran–Mantel–Haenszel test, adjusted for study.

b. Comparison for ew/eow versus ew/pbo.

c. Comparison for ew/ew versus ew/pbo.

Note: Two subjects were randomized in the HiSCR nonresponder strata, although they achieved HiSCR at Week 12.
* denotes $P \leq 0.05$.

AbbVie recommends advising clinicians to periodically assess patients. This assessment should include evidence of benefit (improvement in HS signs and symptoms from baseline value), as well as consideration of potential adverse effects associated with adalimumab treatment, as was done in the clinical studies. This is the basis for AbbVie's recommendation that the statement, '*The benefit and risk of patients on continued long term treatment should be periodically evaluated*', be added to the section on Dosage and Administration of the Humira (adalimumab) PI.

Period B[3] of Studies M11–810 and M11–313 was designed to assess the efficacy and safety of subjects treated with adalimumab after re–randomization to 40 mg qw, 40 mg q2w, or placebo. To minimize the time that subjects received a potentially ineffective dose regimen, a pre–specified criterion was included in the protocol in which subjects were allowed to escape from Period B to the open label extension study (Study M12–555), where they could receive adalimumab 40 mg qw. Subjects who achieved HiSCR at Week 12 were forced to escape from Period B into Study M12–555 if they lost at least 50% of the response they had gained in Period A. Subjects who did not achieve HiSCR at Week 12 were forced to escape if they experienced either worsening of their AN count or an AN count that was equivalent to their baseline AN count at 2 consecutive visits. These criteria established a very low threshold for subjects in all treatment groups to escape from Period B. In addition, subjects who escaped were imputed as non-responders at all subsequent Period B visits. As a result of this escape option, the effect of continuous treatment after a temporary loss of response could not be assessed by focusing solely on Period B data, as that data does not necessarily reflect the benefit of continuous adalimumab treatment beyond Week 12. To assess the benefit of continuous treatment, it is necessary to include results from Study M12–555. All subjects received adalimumab 40 mg qw when they entered Study M12–555. For ease of description, the populations are referenced by the treatment sequence in Period A/Period B/Study M12–555. Twelve weeks after entry into Study M12–555, the HiSCR rate for subjects who received continuous adalimumab qw (qw/qw/qw group) is maintained (Table 10). In addition, the HiSCR rates for subjects who dose re–escalated (qw/q2w/qw group) and for subjects who re–started active treatment (qw/pbo/qw group) ultimately reached a level similar to that of subjects who received

continuous adalimumab qw (qw/qw/qw group). These HiSCR rates were maintained through Week 48 for all 3 groups, supporting the long term benefit of continued adalimumab treatment (Table 10).
In addition, if one assesses those subjects receiving weekly adalimumab at Week 12 who demonstrated at least a 25% improvement in their AN count (that is partial responders and responders) at Week 12, the data demonstrate continued improvement in disease control and maintenance of the HiSCR rate. For subjects who met this criteria and thus were considered at least partial responders, the HiSCR rate at Week 36 was higher in subjects who continued weekly adalimumab than in subjects for whom dosing frequency was reduced to every other week or withdrawn (Table 12). Integrating data from the pivotal studies and Study M12–555, patients who achieved an AN25 after 12 weeks of initial adalimumab treatment and received continuous adalimumab dosing in Period B and/or in Study M12–555, the HiSCR rate at Week 48 was 64.3% after continuous weekly dosing.

Table 12: Number and proportion of AN25 responders who achieved HiSCR[2] at Week 24 and 36 after treatment re–assignment from weekly adalimumab at Week 12

	Subjects, n (%)		
Visit	Placebo (Treatment Withdrawal) N = 73	Adalimumab 40 mg Every Other Week N = 70	Adalimumab 40 mg Weekly N = 70
Week 24	24 (32.9)	36 (51.4)	40 (57.1)
Week 36	22 (30.1)	28 (40.0)	39 (55.7)

AN = abscess and inflammatory nodules; HiSCR = hidradenitis suppurativa clinical response

The consistency of the HiSCR rate for subjects assigned to receive continuous adalimumab every week, for those who received weekly adalimumab irrespective of whether they entered Study M12–555 (that is the qw/qw[qw] group), and for the subset of partial responders (AN25 population), demonstrates the long term benefit of continuous adalimumab treatment and is important information to guide prescribers in the treatment of patients with moderate to severe HS with adalimumab.
AbbVie has proposed the following modifications to the section on Dosage and Administration, Hidradenitis Suppurativa, to reflect that use in HS patients after 12 weeks should be subject to evidence of benefit:

> The recommended Humira (adalimumab)dose regimen for adult patients with HS is 160 mg initially at Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later at Day 15 (given as two 40 mg injections in one day). Two weeks later (Day 29) continue with a dose of 40 mg every week. Antibiotics may be continued during treatment with Humira (adalimumab) if necessary.
>
> In patients without any benefit after 12 weeks of treatment, continued therapy should be reconsidered.
>
> Should treatment need to be interrupted, Humira (adalimumab) may be re-introduced.
>
> The benefit and risk of patients on continued long–term treatment should be periodically evaluated.

Question 2

Sponsor`s response:

There is limited scientific data available on the efficacy of treatments other than adalimumab (for example antibiotics) for patients with HS. AbbVie recommends keeping

the proposed indication language in order to avoid recommending a treatment for which data are not available. Inclusion of such language in the Humira (adalimumab) PI may imply to prescribers a level of data quality/robustness that does not exist for other treatments (for example antibiotics) that may be used to treat patients with HS.

AbbVie appreciates the assessors' consideration to amend the indication statement to reflect second line usage of Humira (adalimumab). While AbbVie maintains its preference, if the assessor does not agree, AbbVie would accept an amended indication, as follows:

> *Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas in adult patients who have had an inadequate response to or are intolerant to antibiotic therapy.*

Advisory committee considerations

In making this recommendation the ACPM;

- noted pivotal studies demonstrated a 20 to 30% responses compared to placebo in first 3 months of weekly adalimumab
- noted no data was submitted for interruption of therapy beyond 36 weeks in patients responding at that time

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Humira solution for injection containing 10 mg, 20 mg and 40 mg adalimumab to have an overall positive benefit–risk profile for the amended indication;

> *Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional HS therapy.*

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- a statement in the DOSAGE AND ADMINISTRATION section of the PI and relevant sections of the CMI should be modified to reflect that use in HS patients after 12 weeks should be subject to evidence of benefit and patients who had not responded by week 12 should discontinue, not treatment to be 'reconsidered'
- a statement in the PI to be reflected in the relevant section of the CMI should refer to trial patients all having had a prior course of antibiotics or had intolerance or contraindication to oral antibiotics.

Specific advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. *Should the PI include specific advice about how and when to measure ongoing treatment benefit, and should ongoing use be contingent on evidence of benefit measured in this way?*

The ACPM noted no good evidence was submitted for new responses after 12 weeks of therapy; however, that for patients that achieve response a reasonable percentage continue to respond up to one year.

The ACPM advised that use beyond 12 weeks should be contingent on evidence of benefit and agreed with the evaluator that 'Ongoing use should be only in those with ≥ 50% reduction from baseline in total abscess and inflammatory nodule (AN) count, with no observed increase in either abscess or draining fistula counts, at Week 12, Week 24 and every 6 months thereafter'.

The ACPM was of the view that treatment should be discontinued (not simply 'reconsidered') in those who have had an inadequate response at 12 weeks.

2. *Is the sponsor's proposed indication wording acceptable, or should the indication specifically reference failure of a trial of systemic antibiotics (or inability to use antibiotics), as per the EU SmPC (but not the US PI)?*

The ACPM noted there was no good evidence of value of antibiotic treatment other than to treat intercurrent infections and, in addition, there are no antibiotics approved for use in this indication in Australia.

However; all patients in the pivotal studies had failed (or were unable to receive) three months antibiotic therapy. This information could be clearly provided in PI (other than the clinical trials section) and in the CMI, for patient information.

The ACPM advised that 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.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Humira adalimumab (rch) 10 mg, 20 mg and 40 mg solution for the new indication:

> *Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional systemic hidradenitis suppurativa therapy.*

Specific conditions of registration

The Humira EU–Risk Management Plan (RMP) 11.3.1, dated June 2015 with ASA Version 5.0 dated September 2015, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Humira approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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