Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Aspirin and Esomeprazole fixed dose combination

Proprietary Product Name: Axanum

Sponsor: AstraZeneca Pty Ltd

August 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>.

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- 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	New fixed combination
Decision:	Withdrawn
Date of Decision:	18 April 2012
Active ingredient(s):	Aspirin + Esomeprazole
Product Name(s):	Axanum
Sponsor's Name and Address:	AstraZeneca Pty Ltd
Dose form(s):	Alma Rd, North Ryde, NSW 2113
Strength(s):	Capsules, hard
Container(s):	81 mg (aspirin) / 20 mg (esomeprazole)
Pack size(s):	Not applicable
Approved Therapeutic use:	Oral (PO)
Route(s) of administration:	Adults: The recommended dose of Axanum is one capsule once daily.
Dosage:	Not applicable
ARTG Number (s)	Aspirin + Esomeprazole

Product background

This AusPAR describes the application by AstraZeneca Pty Ltd to register a fixed dose combination product containing 20 mg esomeprazole and 81 mg aspirin for the initially proposed indication of:

> *For patients who require aspirin and esomeprazole.*
>
> *Axanum is indicated for patients who require aspirin for the prevention of cardiovascular disease (CVD) in combination with esomeprazole for the prevention of ulcers associated with aspirin use.*

The proposed dosing regimen involves oral administration of one capsule (81 mg aspirin/20 mg esomeprazole) once daily, and is indicated for adults (18 years and over).

Aspirin, by irreversibly acetylating cyclo-oxygenase (COX), reduces the production of thromboxane A2 (TXA2) in platelets and prevents platelet aggregation. Aspirin can also reduce prostacyclin (PGI2) production in endothelial cells and cause vasoconstriction. One of the side-effects associated with this use of aspirin is gastrointestinal ulcers. Esomeprazole is a proton pump inhibitor (PPI) which is indicated, amongst other

indications, for the prevention of gastric and duodenal ulcers associated with NSAID therapy (including aspirin therapy).

There are very many drug products containing aspirin which are on the Australian Register of Therapeutic Goods (ARTG) and included among these are a large number of 100 mg strength enteric coated tablets. The latter are the only low-dose aspirin monotherapy drug products on the ARTG (apart from breaking a 300 mg tablet in half which is probably done by a small proportion of patients taking low dose aspirin for cardiovascular protection). Other aspirin monotherapy drug products on the ARTG include 300 mg tablets and dispersible tablets, 320 mg tablets, 324 mg effervescent tablets, 500 mg tablets and dispersible tablets and 650 mg tablets. There are a relatively small number of fixed-dose combination products with aspirin as one of the active ingredients. These include codeine phosphate 8 mg + aspirin 300 mg (such as Aspalgin), clopidogrel 75 mg + aspirin 75 mg or 100 mg (such as Coplavix, Duocover) and dipyridamole 200 mg + aspirin 25 mg (Asasantin SR). These latter fixed-dose combinations are dual combinations where each active component plays an efficacy-related role. In fact these dual combinations have been designed to offer enhanced efficacy with respect to each of the monotherapies.

Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo* with negligible conversion to the R-isomer. In Nexium, the innovator product, it occurs as esomeprazole magnesium trihydrate. Nexium 20 mg and 40 mg tablets are comprised of enteric-coated pellets containing esomeprazole. There are also Nexium 10 mg granules for oral suspension comprised of enteric-coated pellets containing esomeprazole.

Esomeprazole as magnesium trihydrate was first considered by the Australian Drug Evaluation Committee (now called Advisory Committee on Prescription Medicines (ACPM)) in December 2000. The approved indications for Nexium are extensive and occur under 4 main headings, namely 'Gastro-Oesophageal Reflux Disease (GORD)', 'Patients Requiring NSAID therapy[1]', 'Prevention of rebleeding of gastric or duodenal ulcers following treatment with Nexium IV solution by intravenous infusion', 'Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion' and finally 'In combination with appropriate antibiotics for healing of duodenal ulcer associated with *Helicobacter pylori* and eradication of *Helicobacter pylori* in patients with active or healed peptic ulcer'.

From the perspective of this application, the most relevant part of the esomeprazole monotherapy indication is that to do with patients requiring NSAID therapy. The Delegate reproduced in full that part of the indication from the Nexium (esomeprazole) PI and as one can immediately observe the most relevant of the following three components is the third '*Patients requiring NSAID therapy*

1. *Short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy* [with an approved dose of 20 mg once daily and comments that if symptom control has not been achieved after 4 weeks, the patient should be further investigated and that controlled studies did not extend beyond 4 weeks]
2. *Healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy* [the usual dose is 20 mg once daily for 4-8 weeks]
3. *Prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk'* [with an approved dose of 20 mg once daily and a comment that controlled studies did not extend beyond 6 months].

[1] NSAID=non steroidal anti-inflammatory drug

Regulatory status

A similar application was approved in the European Union (EU) (decentralised procedure, 24 countries, completed July 2011).

A similar application was also submitted in the US. The sponsor received an FDA Complete Response Letter (CRL) and subsequently withdrew (24 May 2011) their application a year later due to commercial reasons. This CRL was submitted to, and referred by, the TGA during the evaluation. As the contents of the CRL are not in the public domain these have not been included within this AusPAR.

II. Quality findings

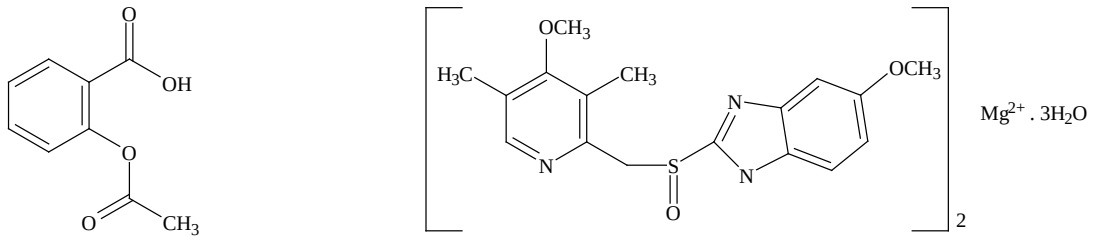
Drug product

Aspirin: An EDQM[2] Certificate of Suitability was provided indicating compliance with the European Pharmacopeia (Ph. Eur)/British Pharmacopeia (BP) monograph for Aspirin. Data was provided to demonstrate that particle size distribution did not require control. The residual solvent acetic acid is controlled to International Conference on Harmonization (ICH) guidance of no more than (NMT) 5000 parts per million (ppm).

Esomeprazole: The esomeprazole magnesium trihydrate is controlled as for the registered Nexium® range of products. The particle size distribution is tightly controlled due the manufacture of the product.

The chemical structures are shown in Figure 1.

Figure 1. Chemical structures.



aspirin

- C9H84O4 MW = 180.2
- CAS # = [50-78-2]
- Slightly soluble in water:
- {1-10 mg/mL}

esomeprazole magnesium trihydrate

- C34H36N6O6S2Mg.3H2O MW = 767.2
- CAS # = [217087-09-7]
- sparingly soluble in water
- {10-33 mg/mL}

Axanum capsules

The process (which involves multiple coating steps) was adequately validated and included appropriate in-process controls.

The capsules are well controlled with expiry limits for the esomeprazole and aspirin assays and degradants of aspirin and esomeprazole meeting ICH requirements.

[2] The European Directorate for the Quality of Medicines & HealthCare (EDQM) protects and promotes public and animal health in Europe.

Overall the stability data supported a shelf life of 2 years when stored below 25ºC in polyamides (PA)/Aluminium (Al)/polyvinyl chloride (PVC)/Al blister packs.

The chemistry and quality control aspects of the draft PI have been finalised to the satisfaction of the quality evaluator. As have the carton and blister foil labels and the Provisional ARTG Record[3].

Biopharmaceutics

The pivotal Phase III efficacy studies were performed with monotherapy products: US available aspirin tablets from Bayer and US available Nexium capsules (not registered in Australia).

To support registration, one bioavailability study was provided together with a number of justifications for not providing bioavailability data.

Results

Study D961FC00002 compared a 325/40 mg formulation of the fixed dose combination capsules to the monotherapy aspirin tablets and esomeprazole capsules used in the Phase III efficacy studies (325 mg aspirin tablets of Bayer bought in the US and 40 mg Nexium capsules registered in the US). This was performed in the fasted state. The results indicate bioequivalence of the two treatments with respect to all three analytes.

One acceptably validated bioanalytical test method was used for the determination of aspirin (acetyl salicylic acid) and salicylic acid and another for the determination of esomeprazole. The esomeprazole assay was non-enantiospecific but this was justified as no racemisation or inversion occurs in vivo.

Justification for the use of a 325/40 mg capsule rather than the proposed 81/20 mg capsule

Both the aspirin and esomeprazole components of the proposed for 81/20 mg capsule and the 325/40 mg capsule used in the bioavailability study were proportional and the two products had similar dissolution profiles at pH 2, 4.5 and 6.8.

Further it was shown that there are no pharmacokinetic interactions between esomeprazole and aspirin.

Justification for the use of an overseas aspirin comparator rather than an Australian aspirin comparator

Aspirin is BCS Class I[4] in doses up to ~500 mg and the dissolution profiles of an Australian immediate release tablets (DBL, now Mayne Pharma) were similar to those of the US Pharmacopeia (USP) aspirin tablets used in the Phase III clinical studies and the bioavailability study and also to the proposed fixed dose combination capsules.

Justification for being able to switch directly from Nexium tablets to the proposed product

The esomeprazole pellets used in the combination capsule are similar in formulation to the pellets used in the Australian registered Nexium granules for oral suspension and the

[3] The Good Manufacturing practice (GMP) Clearances for the overseas manufacturers are valid until at least 12 October 2012.

[4] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Nexium capsules used in the Phase III clinical and bioequivalence study. The Nexium tablets registered in Australia contain coated pellets of esomeprazole which have the same coating ingredients as the encapsulated pellets but include a thicker enteric coating and an additional layer to survive tablet compression. The TGA has previously evaluated data that demonstrated bioequivalence of the Nexium tablets and the Nexium granules for oral suspension (the 90% confidence interval (CI) were 89 101% and 94-104% for the peak plasma concentration (Cmax) and the area under the plasma concentration time curve (AUC), respectively). In addition, the tablets and granules were both 94-99% dissolved in 30 minutes; the same as the proposed product.

Justification for the lack of a study with food

Although the effect of food on esomeprazole delays and reduces absorption, it does not affect the affect on gastric pH (see the Nexium PI).

As a BCS class I compound aspirin is completely absorbed from the gut. In the combination capsule, aspirin is formulated as an immediate release formulation and other immediate release aspirin formulations are administered without regard to food intake. In addition, the release of aspirin from the proposed combination capsule is slower at 15 minutes at low pH (42%) than pH 4.5 and 6.8 (62%). Therefore, since food increases pH it would be expected to improve dissolution of aspirin from the capsule and no effect on absorption is expected.

Justification for the lack of an absolute bioavailability study

The absolute bioavailability of esomeprazole and aspirin from monotherapy products are known and Study D961FC00002 indicates that the bioavailability is not changed in the proposed products.

Advisory committee considerations

This application was presented to the 140th meeting of the Pharmaceutical Subcommittee of ACPM (PSC) in August 2011. The PSC had no objections to approval of the submission provided all outstanding issues were addressed to the satisfaction of the TGA (*which was the case*), and did not require to review this submission again. In particular the Committee considered the bioavailability data submitted in support of the submission were sufficient to support the dosing instructions in the PI and accepted the sponsor's justifications for:

- Using an overseas sourced aspirin tablet as a comparator in the clinical trial and bioavailability studies.
- Why the results from the pivotal bioavailability/bioequivalence study that compared a 325 mg / 40 mg aspirin / esomeprazole capsule to a 325 mg aspirin tablet and a 40 mg esomeprazole capsule both used in the clinical trial studies should be extrapolated to the 81 mg / 20 mg aspirin / esomeprazole capsule formulation proposed for registration.
- Considered the lack of bioavailability data comparing the proposed capsule to the enteric coated esomeprazole tablets registered in Australia to be acceptable considering the proposed use of the combination product.

The PSC also recommended some amendments to the PI.

Quality summary and conclusions

Approval of this submission was recommended with respect to chemistry and manufacturing control.

With respect to bioavailability:

- Study D961FC00002 showed bioequivalence of a 325/40 fixed dose capsule to the monotherapies used in the Phase II clinical studies and it was accepted that this could be extrapolated to the proposed 81/20 capsule.
- It was accepted that the US aspirin product used in the Phase III clinical studies and the bioavailability study could be used as a surrogate comparator rather than an Australia aspirin product.
- It was accepted that patients may switch from Australian 20 mg Nexium tablets to the proposed fixed dose combination product without a change in the bioavailability of esomeprazole.
- It was also accepted that no bioavailability studies were required to investigate the absolute bioavailability and effect of food in relation to the fixed dose combination capsules.

III. Nonclinical findings

Introduction

General comments

According to the EU Guideline on the nonclinical development of fixed combinations of medicinal products (which has been adopted by the TGA), when the fixed combination under development includes compounds for which there is sufficiently documented human experience of their individual and combined use, safety studies in animals are, in general, not required[5]. Esomeprazole (20 mg/day) is already approved for prevention of gastric and duodenal ulcers associated with NSAID (non-selective and cyclo-oxygenase-2 (COX-2) selective) therapy in patients at risk. Low dose (100 mg) aspirin formulations are available as over-the-counter (OTC) medicine with indications including "*For the treatment of patients with known cardiovascular or cerebrovascular disease, as an antiplatelet agent for prophylaxis against acute myocardial infarction, unstable angina, transient ischaemic attack and cerebrovascular accident (stroke)*". The proposed dosage levels of Axanum are within the range of those recommended for the individual components. Thus, the safety of the proposed dosage levels of the individual components has been established in previous nonclinical studies and (in the case of aspirin) with extensive clinical use. However, the sponsor has provided new Good Laboratory Practice (GLP) compliant studies in dogs (up to 3 months, with a 3 month recovery period) comparing the toxicity and toxicokinetics of esomeprazole in combination with aspirin with those of the individual agents. The sponsor also submitted data previously evaluated in support of the registration application for esomeprazole.

Pharmacology

Pharmacodynamic interactions

Esomeprazole (Nexium®) is the pure S-enantiomer of the racemic proton pump inhibitor (PPI) omeprazole. The pharmacodynamic effects of the enantiomers do not differ from each other or from the racemate in vitro. Esomeprazole was developed as it was believed to have an improved pharmacokinetic profile compared with the racemate.

[5] Guideline on the Non-Clinical Development of Fixed Combinations Of Medicinal Products. EMEA/CHMP/SWP/258498/2005. http://www.tga.gov.au/pdf/euguide/swp25849805final.pdf

Aspirin has a long history of therapeutic use, not only for its analgesic, antipyretic and anti-inflammatory properties but also for its anti-thrombotic properties, which are of value in states of platelet hyperaggregability. Aspirin binds irreversibly to the enzyme cyclo-oxygenase-1 (COX-1) in platelets, leading to its antiplatelet effect. Side effects of aspirin treatment are mainly dyspeptic symptoms, gastrointestinal (GI) lesions and increased gastrointestinal and overall bleeding, which are consequences of the blockage of prostaglandin synthesis through inhibition of various COX enzymes. This leads to a decrease in mucosal protection, which in turn predisposes the patient to mucosal lesions such as peptic ulcers and peptic ulcer bleeding.

No data were submitted on potential pharmacodynamic interactions of the combination, and the potential for interaction will need to rely on the clinical data.

Pharmacokinetics

Published data indicate that aspirin is well absorbed from the GI tract in humans by a process of passive diffusion of the unionised drug in the stomach and particularly the upper small intestine (Drugdex® evaluation for Aspirin, Micromedex® 1.0 Healthcare Series, updated 31.1.11, Thomson Reuters). Absorption is delayed by concurrent food intake, and its rate is increased at low gastric pH. Aspirin is quickly hydrolysed by esterases in the liver and to a lesser extent in plasma and erythrocytes to salicylic acid and is essentially undetectable in plasma 1-2 h after dosing. The amount of unhydrolysed aspirin in plasma has been found to correlate with the duration of analgesic efficacy.

Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex and lungs. The protein binding of salicylate is nonlinear. At low concentrations (<100 µg/mL), approximately 90% of plasma salicylate is bound to albumin but this reduces to about 75% at concentrations > 400 µg/mL. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an aryl glucuronide and a number of minor metabolites, and has a plasma half life of approximately six hours. It has been reported that salicylic acid is subject to aromatic hydroxylation by CYP2E1[6,7].

A toxicokinetic study in dogs administered aspirin once or twice daily for up to 28 days confirmed the rapid absorption and hydrolysis of aspirin in this species. The median time to peak plasma concentration (T_{max}) was about 1 h for aspirin and 2-3 h for salicylic acid. Since aspirin is rapidly hydrolysed and plasma concentrations were associated with a high level of inter-individual variability, the systemic exposure to salicylic acid was assessed in the nonclinical studies. Because of this, it was not possible to directly determine any possible effect of esomeprazole coadministration on aspirin exposure.

Previous studies showed that in human liver microsomes, esomeprazole is metabolised by cytochrome P450 (CYP) isozyme 2C19 to the hydroxy and 5-*O*-desmethyl metabolites and by CYP3A4/5 to the sulphone. It is also an inhibitor of CYP2C19 but the CYP isozymes responsible for esomeprazole metabolism in dogs have not been confirmed.

Toxicokinetic data were provided from repeat dose toxicity studies in dogs given esomeprazole and aspirin alone and in combination. The Tmax for esomeprazole and aspirin were similar whether administered alone or in combination. The systemic exposure to esomeprazole when given alone was lower after repeated dosing than after a

[6] Dupont, I et al (1999). Involvement of Cytochromes P-450 2E1 and 3A4 in the 5-hydroxylation of salicylate in humans. *Drug Metabolism and Disposition* **27:** 322-6.
[7] Wu, D & Cederbaum, A.I. (2001). Sodium salicylate increases CYP2E1 levels and enhances arachidonic acid toxicity in HepG2 cells and cultured rat hepatocytes. *Molecular Pharmacology* **59:** 795-805.

single dose, which is in agreement with previously evaluated studies. Systemic exposure when esomeprazole was administered in combination with aspirin was approximately 25% lower than when administered alone. Although the CYP isozymes involved in esomeprazole metabolism in dogs are not known, Chen et al[8] reported that low-dose aspirin reduced the *in vivo* activity of CYP2C19 in healthy male subjects.

The plasma kinetics of aspirin and/or its metabolite salicylic acid were examined in two 13 week repeat dose studies in dogs. Systemic exposure to salicylic acid increased in proportion to increases in aspirin dose despite the co-administration of esomeprazole. Co-administration with esomeprazole in one study reduced the exposure to salicylic acid by 50-68% but not in another study. A reduction in salicylic acid exposure could be explained by the finding that CYP1A1/2 and CYP2E1 activities were induced by esomeprazole, since salicylic acid is metabolised by CYP2E1 via aromatic hydroxylation[6, 7]. However, in neither study were plasma concentrations of aspirin determined (owing to its rapid hydrolysis in plasma and the large inter-individual variability). Therefore, no firm conclusions can be drawn as to whether or not the co-administration of esomeprazole would reduce the systemic exposure to aspirin sufficiently to reduce efficacy. However, given that aspirin is hydrolysed by multiple esterases, it is unlikely that esomeprazole would inhibit all of these and therefore it is unlikely that esomeprazole would affect the conversion of aspirin to salicylic acid.

Cytochrome P450 and b5 enzyme activities were measured in liver microsomes prepared *post mortem* in the 3 month study. Esomeprazole administration, either alone or in combination with aspirin, increased the activity of CYP1A1/2 and CYP2E1, the latter being involved in the metabolism of salicylic acid. This could account for the reduction in systemic exposure to salicylic acid when aspirin and esomeprazole were administered in combination. However, it would not necessarily mean that systemic exposure to aspirin was reduced. It is noted that there was no reduction in systemic exposure to aspirin or salicylic acid in Clinical Study D961FC00001 when 325 mg of aspirin was administered with and without 40 mg esomeprazole.

Toxicology

The sponsor submitted a number of dose range-finding and toxicokinetic studies in dogs with aspirin and esomeprazole alone and in combination. The doses administered in the 3 month pivotal study were selected on the basis of the results of these studies and were judged to be considerably lower than the maximum tolerated dose, while still providing clear toxic effects. The higher dose levels were generally administered as two daily doses separated by 4 h to reduce the risk of severe CNS effects such as convulsions, which were previously observed in repeat dose studies with esomeprazole and/or its racemate, omeprazole and which are known to be directly related to the magnitude of C_{max}. In addition, this reduced the practical difficulties of dosing with large volumes or numbers of capsules in a single dose. In the preliminary studies, higher doses of esomeprazole were associated with severe CNS effects, while gastric ulceration, with or without bleeding, was observed with higher doses of aspirin.

In the pivotal 3 month study, toxic effects of esomeprazole at 42 mg/kg/day (2x21 mg/kg 4 h apart) in both sexes included the following:

- Transient or sporadic mild CNS effects (decreased activity, hunched posture, lying on side, cold to touch, partly closed eyes, uncoordinated, abnormal gate, decreased muscle tone, tremors and head shaking);

[8] Chen, X.-P. et al (2003). Isozyme-specific induction of low-dose aspirin on cytochrome P450 in healthy subjects. *Clinical Pharmacology & Therapeutics* **73:** 264-71.

- A low incidence of emesis and abnormal faeces;
- Minor reductions in body weight gain, associated with reduced food consumption;
- A number of short-lived gastric erosions/lesions/ulcers, sometimes accompanied by bleeding, on endoscopic examination in a few animals;
- Minor reductions in erythrocytic parameters;
- Minor changes in serum chemistry (reduced total protein and increased cholesterol);
- A 50% increase in gastric weight, without any associated histopathological changes ;
- Increased CYP1A1/2 and CYP2E1 activity

These effects were consistent with previously evaluated repeat dose studies in dogs with Omeprazole and esomeprazole.

Treatment of aspirin alone was associated with the following signs of toxicity:

- Emesis, abnormal faeces and mild CNS signs (tremors and head shaking) but at a much lower incidence than in the groups treated with the highest dose of esomeprazole;
- Small decreases in erythrocytic and serum iron parameters and a reduction of haemosiderin deposits in the liver or spleen;
- A number of short-lived gastric erosions/lesions/ulcers, sometimes accompanied by bleeding, on endoscopic examination.

No treatment-related histopathological findings were noted in any study, including in those animals that had exhibited gastric lesions during endoscopic examination.

There was no evidence of any new or unexpected toxicological effect when esomeprazole and aspirin were co-administered and the incidence and severity of toxic effects were consistent with additivity. In a further 3 month repeat-dose study with a 3 month post dosing recovery period, all of the signs of toxicity described above were shown to be reversible, or were tending towards recovery.

Relative exposure

In selecting the doses of esomeprazole and aspirin for the pivotal 3 month study in dogs the aim was to ensure that the exposure levels for esomeprazole and aspirin (or its metabolite, salicylic acid) were in the same proportion as those anticipated in humans with therapeutic use of the proposed fixed dose combination, and also that the exposures of the individual components were several fold higher.

Table 1. Comparison of non clinical and clinical exposures

Species	Study duration	Dose (mg/kg/day PO)		AUC[a] (µmol·h/L)		Rel. Exposure ESO/SA	Dog: human Exposure ratio[b]	
		Eso	Aspirin	Eso	SA		ESO	SA
Dog (beagle)	90 days (day 85)	14	14	33	750	0.044	5	4.7
		42[c]	42[c]	48	1900	0.025	7	12
		42[c]	-	61	-	-	-	-
		-	42[c]	-	3100	-	-	-
		Dose (mg)						
Human[e] (healthy volunteers)	5 days (day 5)	20[d]	81[d]	6.5[d]	160[d]	0.041[d]	-	
		40	325	13	630	0.021		
		40	-	13	-	-		
		-	325	-	640	-		

[a]$AUC_{0\text{-}24h}$ in dogs, AUC_{τ} in humans

[b]Dog:human plasma AUC (comparing plasma AUC in the repeat dose toxicity studies in dogs with the anticipated clinical AUC, extrapolated from study D961FC00001)

[c]Administered as 2 doses of 21 mg, 4 h apart

[d]Extrapolated from the results in Study D961FC00001

[e]Values taken from Study D961FC00001, 5 days repeated dosing 40 mg ESO plus 325 mg aspirin, given as a free combination of ESO capsule + aspirin tablet.

ESO= esomeprazole. SA= salicylic acid

Relative exposure levels in the pivotal dog study are shown above in Table 1. It should be noted that the human data is taken from a study in which esomeprazole and aspirin were taken as separate components and not with the proposed formulation. Also, the doses of the two actives in the clinical study were higher than for the proposed formulation. The human exposure data was therefore extrapolated to the proposed clinical doses in for comparison with the animal data. In addition, salicylic acid exposure was used as a surrogate for aspirin, owing to the rapid hydrolysis of aspirin in dog plasma. The exposure comparisons shown in the relative exposure table above indicate that the ratio of esomeprazole to salicylic acid systemic exposures in the 3 month toxicity study in dogs were comparable to the predicted ratios in humans with the proposed combination. The animal:human exposure ratios for esomeprazole and salicylic acid in the 3 month dog study compared with the extrapolated values from the clinical study were 7 and 12, respectively.

Pregnancy classification

The sponsor has proposed P**r**egnancy Category C[9]. This is in keeping with the pregnancy categorisation of aspirin alone; esomeprazole is in Category B3.

[9] Category C. Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details. Category B3. Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Paediatric use

Axanum is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- As the two individual components are currently available in free combination, nonclinical data on the combination are generally not required[5]. However, the sponsor provided new GLP compliant studies in dogs (up to 3 months, with a 3 month recovery period) comparing the toxicity and toxicokinetics of esomeprazole in combination with aspirin with those of the individual agents.
- No data were submitted on potential pharmacodynamic interactions of the combination, and the potential for such interaction will therefore rely on the clinical data.
- In the 3 month repeat dose studies in dogs, systemic exposure to esomeprazole when administered in combination with aspirin was approximately 25% lower than when administered alone.
- No firm conclusions could be drawn from the nonclinical data on the possible effect of esomeprazole co-administration on systemic exposure to aspirin in dogs.
- The ratio of systemic exposures to esomeprazole and salicylic acid in the 3 month toxicity study in dogs were comparable to the predicted ratios in humans with the proposed combination.
- There was no evidence of any new or unexpected toxicological effect when esomeprazole and aspirin were co-administered and the incidence and severity of toxic effects were consistent with additivity.
- Both active substances have been approved and marketed for many years and there are extensive nonclinical and clinical data available for the individual components. Furthermore, esomeprazole is currently approved to be used in free combination with aspirin for the proposed indication. In conclusion, there are no nonclinical objections to the registration of Axanum.
- Amendments to the PI were recommended.

IV. Clinical findings

Introduction

The objective of the Axanum development program was to demonstrate superior efficacy for peptic ulcer prophylaxis compared with placebo in patients receiving long-term low dose aspirin (ASA) for the primary and secondary prevention of cardiovascular disease (CVD).

Study D961FC00011 examined platelet aggregation and serum thromboxane B2 (TXB2) in a pharmacodynamic (PD) drug-drug interaction study. Esomeprazole had no effect on platelet function.

Key studies

Two randomised, double-blind, 26 week, safety and efficacy, Phase III studies were performed to compare esomeprazole 20 mg with placebo (Study D9617C00011); or

esomeprazole 20 mg and 40 mg given once daily (Study D961F00003) compared with placebo in 2417 evaluable patients receiving continuous low-dose ASA.

A drug interaction study (D961F00001) was performed to investigate potential interaction between esomeprazole and ASA. This trial was conducted using the highest proposed doses of study medication, esomeprazole 40 mg once a day (od) and ASA 325 mg od.

The Phase III studies were performed using a free combination of a clinical trial esomeprazole capsule (or matching placebo) and commercially available ASA tablets. Evidence of bioequivalence between the fixed dose and free combination of esomeprazole and ASA was investigated in Study D961F00002. This trial was also performed using the highest proposed doses of study medication, esomeprazole 40 mg od and ASA 325 mg od.

Good Clinical Practice (GCP) aspects

The studies complied with ICH/GCP guidelines and applicable local regulations. The studies were monitored according to AstraZeneca internal quality control and internal audit processes.

Pharmacokinetics

Introduction

Two studies examined the pharmacokinetics of Axanum in 104 healthy subjects (67 female), aged 20 to 50 years.

Methods

Analytical methods

ASA and SA levels in blood were determined using a validated method (PBR-065833), which following protein precipitation utilised high performance liquid chromatography with ultraviolet (UV) detection. The lower limits of quantification (LLOQ) for ASA and SA in plasma were 0.555 µmol/L and 3.62 µmol/L, respectively. Esomeprazole levels were also determined using a validated method (PBR-065373), which utilised liquid-liquid extraction, normal phase liquid chromatography and UV-detection according to method BA-517-01 (PBRL-BV-838). The LLOQ for esomeprazole was 0.025 µmol/L.

Pharmacokinetic data analysis

Pharmacokinetic parameters were derived using non-compartmental methods in WinNonlin® Professional Version 5.2 (Pharsight Corp., Mountain View, California).

Statistical analysis

Statistical analyses were performed using SAS software, version 9.1. The log-transformed variables of AUC and Cmax were analysed using a mixed model analysis of variance (ANOVA) with fixed effects for sequence, period and treatment and a random effect for subject within sequence.

Absorption

Bioavailability

Not applicable.

Bioequivalence

A Phase I open-label, randomised, single-centre, 2-stage group sequential design, 2-way crossover bioequivalence study (D961FC00002) compared the pharmacokinetics of

- a fixed-dose combination capsule of esomeprazole 40 mg and low-dose acetylsalicylic acid 325 mg (Treatment A) with
- a free combination of esomeprazole capsule 40 mg and low-dose acetylsalicylic acid tablet 325 mg (Treatment B)

following a single oral dose in 49 healthy subjects (29 female), aged 20 to 50 years. All 49 subjects were included in the PK analysis; however, only those subjects who completed both treatments (46 subjects) were included in the statistical comparisons of the PK data. Blood samples for the determination of PK parameters were taken predose and up to 12 hours postdosing. The median Tmax, mean half life ($t_{1/2}$), AUC and C_{max} of esomeprazole, ASA and SA were similar for the fixed and free combinations (Table 2). Treatments A (esomeprazole and ASA combination capsule) and B (esomeprazole capsule + ASA tablet) were bioequivalent in regards to the primary PK variables (AUC and C_{max} of esomeprazole and ASA) (Table 3). For esomeprazole, the geometric least-squares (GLS) mean ratios for AUC and C_{max} were 96.6 (94% CI: 90-103.8) and 99.1 (CI: 90.2-108.9), respectively. Whereas for ASA the GLS mean ratios were 103.9 (94% CI: 99.6-108.3) and 101.9 (CI: 91.7-113.2) for AUC and Cmax, respectively. Similarly, for the secondary exposure-related PK variables (AUC_t of esomeprazole and ASA, and AUC, AUC_t, and C_{max} of SA) the GLS mean ratios for all the parameters were within a range of 95.4 to 103.9% and CIs were therefore within the 80 to 125% acceptance range for bioequivalence.

Table 2. Study D961FC00002

Summary of Esomeprazole, Acetylsalicylic Acid, and Salicylic Acid Pharmacokinetic Parameters by Treatment

Analyte	Parameter	Mean (SD) Treatment A (N = 47)	Mean (SD) Treatment B (N = 48)
Esomeprazole	AUC (µmol*h/L)	6.190 (3.412)	6.530 (3.798)
	AUC_t (µmol*h/L)	6.112 (3.388)	6.459 (3.780)
	C_{max} (µmol/L)	3.130 (1.419)	3.121 (1.423)
	t_{max} (h) [a]	3.00 (1.25, 4.00)	3.00 (1.25, 5.00)
	$t_{1/2\,\lambda z}$ (h)	0.8940 (0.3293)	0.9281 (0.3765)
Acetylsalicylic Acid	AUC (µmol*h/L)	24.69 (5.41)	23.90 (5.26)
	AUC_t (µmol*h/L)	23.97 (5.36)	23.32 (5.35)
	C_{max} (µmol/L)	17.93 (5.43)	18.03 (6.11)
	t_{max} (h) [a]	0.75 (0.33, 2.25)	0.50 (0.33, 3.00)
	$t_{1/2\,\lambda z}$ (h)	0.4624 (0.1524)	0.4050 (0.1440)
Salicylic Acid	AUC (µmol*h/L)	671.1 (159.0)	691.6 (174.8)
	AUC_t (µmol*h/L)	645.6 (145.5)	663.6 (161.0)
	C_{max} (µmol/L)	123.6 (22.1)	130.6 (25.6)
	t_{max} (h) [a]	2.25 (1.50, 3.50)	2.13 (1.25, 4.00)
	$t_{1/2\,\lambda z}$ (h)	2.051 (0.410)	2.104 (0.401)

Treatment A = Esomeprazole 40 mg and low-dose ASA 325 mg combination capsule given as a single dose.
Treatment B = Esomeprazole 40 mg capsule + low-dose ASA 325 mg tablet, given as a single dose.
a) Data presented for this parameter are median (minimum, maximum).
N – number of subjects and number of observations; SD – standard deviation.

Table 3. Study D961FC00002

Results of Statistical Comparisons of Key Esomeprazole, Acetylsalicylic Acid, and Salicylic Acid Pharmacokinetic Parameters

	Treatment A (N = 46)		Treatment B (N = 46)		Statistical Comparison (Treatment A/B) [a]	
Parameter	GLS Mean	95% CI	GLS Mean	95% CI	Ratio	94% CI
Esomeprazole						
AUC (µmol*h/L)	5.327	(4.456, 6.368)	5.513	(4.612, 6.591)	96.6	(90.0, 103.8)
AUC_t (µmol*h/L)	5.249	(4.385, 6.284)	5.440	(4.544, 6.512)	96.5	(89.8, 103.7)
C_{max} (µmol/L)	2.821	(2.456, 3.240)	2.845	(2.477, 3.268)	99.1	(90.2, 108.9)
Acetylsalicylic Acid						
AUC (µmol*h/L)	24.14	(22.55, 25.84)	23.24	(21.71, 24.88)	103.9	(99.6, 108.3)
AUC_t (µmol*h/L)	23.42	(21.84, 25.12)	22.63	(21.09, 24.27)	103.5	(99.2, 108.0)
C_{max} (µmol/L)	17.20	(15.53, 19.06)	16.89	(15.24, 18.71)	101.9	(91.7, 113.2)
Salicylic Acid						
AUC (µmol*h/L)	653.1	(606.2, 703.7)	661.5	(613.9, 712.6)	98.7	(95.5, 102.1)
AUC_t (µmol*h/L)	629.4	(585.4, 676.8)	636.2	(591.6, 684.1)	98.9	(95.8, 102.2)
C_{max} (µmol/L)	121.3	(114.3, 128.7)	127.2	(119.9, 134.9)	95.4	(91.9, 99.0)

Treatment A = Esomeprazole 40 mg and low-dose ASA 325 mg combination capsule given as a single dose.
Treatment B = Esomeprazole 40 mg capsule + low-dose ASA 325 mg tablet, given as a single dose.
a) Results presented are GLS mean ratios and 94% CIs.
Note: Results are based on a linear mixed effect model with terms for treatment, sequence, and period as fixed effects and subject within sequence as a random effect. For each parameter, subjects had to have values for both treatments to be included in the analysis.
CI – confidence interval; N – number of subjects and number of observations; GLS – geometric least-squares.

Justification provided for requesting a waiver for a study examining the bioequivalence of the fixed and free combinations of 20/81 mg esomeprazole/ASA.

Esomeprazole is well absorbed following oral administration, although it is subject to first pass metabolism. This first-pass metabolism gives rise to the observed dose-dependent pharmacokinetics with greater than dose proportional increases in AUC being observed at doses of greater than 10 mg. The usual dose range for esomeprazole is 20 mg to 40 mg once a day and it is not regarded as an active pharmaceutical ingredient which has a narrow therapeutic index.

ASA is highly soluble and membrane permeable, and has been classified by the World Health Organization (WHO) as a BCS Class I compound (WHO Technical Report Series, No. 937, 2006, Annex 8). It is susceptible to degradation in the GI tract and first-pass metabolism. ASA is considered to have uncomplicated dose-linear pharmacokinetics over a broad dose range and is not regarded as an active pharmaceutical ingredient which has a narrow therapeutic range.

Accordance with FDA guidelines

The highest strength of the fixed-dose combination capsule (325 mg/40 mg) under development was chosen for the bioequivalence study based on FDA guidance (FDA Guidance for Industry 2003) as well as EMEA guidance (Note for Guidance on the Investigation of Bioavailability and Bioequivalence 2001, and Draft Guidance on the Investigation on Bioequivalence 2008), which is applicable for pharmaceutical ingredients demonstrating dose-linear or greater than dose-linear pharmacokinetics.

See also *Quality findings* above.

Conclusion

Based on the preceding information, the evaluator believed that a waiver for a bioequivalence study examining the fixed and free combinations of 20/81 mg esomeprazole/ASA was justified.

Intra and inter individual variability

In bioequivalence Study D961FC00002, the model estimates of inter-subject CV for AUC, AUC_t and C_{max} ranged from 24% to 63% for esomeprazole, 21% to 23% for ASA, and 18% to 24% for SA. For intra-subject CV the corresponding values ranged from 18% to 24%, 10% to 27% and 8% to 9% for esomeprazole, ASA and SA, respectively.

Interactions

In vivo pharmacokinetic interactions

A single-centre, open, randomised, three-way crossover drug-drug interaction study (Study D961FC00001) examined the pharmacokinetic interaction between 40 mg esomeprazole capsules and 325 mg low-dose acetylsalicylic acid tablets following 5 days of repeated oral administration in 55 healthy subjects (38 female), aged 20 to 49 years. Each treatment period was separated by a wash-out period of at least 13 days, counted from the last day of dosing and blood samples for the PK assessment of esomeprazole, ASA and SA were taken pre-dose and up to 12 hours post-dose on Day 5 of each treatment period. The ratios of the geometric means for esomeprazole AUC_t and $C_{ss,max}$ following co-administration of esomeprazole with ASA and esomeprazole alone were 0.93 (90% CI: 89-98) and 0.96 (90% CI: 91-101), respectively (Table 4). Similarly, the ratios of the geometric means for ASA AUC_t and peak plasma concentration at steady state ($C_{ss,max}$) when given in combination with esomeprazole and when administered alone were 1.04 (90% CI: 100-109) and 1.12 (90% CI: 103-122), respectively. For SA, the ratios were 0.99 (90% CI: 95-102) and 1.02 (90% CI: 98-106) for SA AUC_t and $C_{ss,\,max}$, respectively. These results indicate that there was no PK interaction between the two drugs.

As part of this study the subjects were also genotyped; however, all but one subject were genotyped as extensive metabolisers of CYP2C19; therefore, as only one subject was classified as a poor metaboliser of CYP2C19, no conclusions could be drawn on the affect of this characteristic upon the drug-drug interaction studied.

Evaluator's overall conclusions on pharmacokinetics.

- The free combination of 40 mg esomeprazole capsules and 325 mg aspirin tablets was bioequivalent to the fixed-dose combination capsule of esomeprazole 40 mg and low-dose acetylsalicylic acid 325 mg. This study is relevant for the proposed formulation (that is, the fixed-dose combination capsule containing 81 mg aspirin and 20 mg esomeprazole) as the two fixed-dose formulations have: similar *in vitro* dissolution profiles; the same manufacturing process and excipients; the same proportion of excipients to active drug; and the bioequivalence study has been conducted at the highest dose in development as per FDA and EU guidance.
- There was no PK interaction between esomeprazole, ASA and SA.

Table 4. Study D961FC00001

Estimated ratios of geometric means with 90% CI for pharmacokinetic variables of esomeprazole, ASA and SA following repeated oral administration of esomeprazole capsule 40 mg o.m. (A) or ASA 325 mg o.m. (B) or a combination of esomeprazole capsule 40 mg o.m. and ASA 325 mg o.m. (C). Per Protocol population

					90 % CI	
Variabel	Ratio		Number of subjects	Estimate	lower	upper
Esomeprazole	Esomeprazole with ASA/ Esomeprazole alone (C/A)	AUC_τ	52	0.93	0.89	0.98
	Esomeprazole with ASA/ Esomeprazole alone (C/A)	AUC_t	52	0.93	0.89	0.98
	Esomeprazole with ASA/ Esomeprazole alone (C/A)	$C_{ss,\,max}$	52	0.96	0.91	1.01
ASA	ASA with esomeprazole/ ASA alone (C/B)	AUC_τ	49	1.04	1.00	1.09
	ASA with esomeprazole/ ASA alone (C/B)	AUC_t	51	1.04	1.00	1.09
	ASA with esomeprazole/ ASA alone (C/B)	$C_{ss,\,max}$	51	1.12	1.03	1.22
SA	ASA with esomeprazole/ ASA alone (C/B)	AUC_τ	51	0.99	0.95	1.02
	ASA with esomeprazole/ ASA alone (C/B)	AUC_t	51	0.99	0.95	1.02
	ASA with esomeprazole/ ASA alone (C/B)	$C_{ss,\,max}$	51	1.02	0.98	1.06

Pharmacodynamics

Introduction

A single study examined the pharmacodynamics of esomeprazole and aspirin free combination.

Mechanism of action

Aspirin inhibits the formation of a precursor for TXA2, which is a short-lived inducer of platelet aggregation and a potent vasoconstrictor. Esomeprazole is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell where it inhibits the enzyme H+K+-ATPase (the acid pump), which is responsible for both basal and stimulated acid secretion.

The primary and secondary variables examined in the pharmacodynamic (PD) drug-drug interaction study (D961FC00011) were platelet aggregation and serum TXB2.

Pharmacodynamic interactions with other medicinal products or substances.

A Phase I, open, two-way crossover, drug-drug interaction study (Study D961FC00011) evaluated the effect of esomeprazole on the pharmacodynamics of acetylsalicylic acid after 5 days of treatment in 29 healthy subjects (8 female), aged 19 to 75 years. Platelet aggregation was measured using the VerifyNow-ASA point-of-care platelet function test (Accumetrics), which the FDA has found to be substantially equivalent to previously cleared automated platelet aggregation devices[10]. The results of this test are expressed as Aspirin Reactivity Units (ARU) and the pre-specified therapeutic range established by the

[10] www.accessdata.fda.gov/cdrh_docs/pdf4/k042423.pdf

manufacturer as indicative of reduced platelet activity attributable to ASA is 350 to 550 ARU. TXB2 was measured in serum using TXB2 EIA kit provided by Cayman chemical. It has been reported that 99% inhibition[11] of thromboxane is necessary to achieve optimal platelet suppression. Both assays were performed according to the manufacturer's instructions.

The effect of esomeprazole was assessed by examining the relative change in the VerifyNow Aspirin assay after 5 days of treatment, relative to baseline (Day 1). Each subject was randomly assigned to receive aspirin alone (Period 1) for 5 days followed by treatment with esomeprazole in combination with aspirin (Period 2) for 5 days, or vice-versa, with at least a 14 day wash-out period between treatments. There was little difference in the effect of treatment on platelet aggregation, as measured by ARU, when aspirin was given alone (delta ARU from day one to day 6 = 0.7001) or in-combination with esomeprazole (delta ARU = 0.7146).

Similarly there was little difference in the effect of aspirin on TXB2 concentrations when given alone or in combination with esomeprazole (Day 6/Day 1 ratios of 0.0041 and 0.0045, respectively). Least squares analysis of the data indicated that there was no difference in the anti-platelet activity of aspirin when given alone or in combination with esomeprazole.

Genetic differences in pharmacodynamic response

Not applicable.

Evaluator's overall conclusions on pharmacodynamics

Esomeprazole did not affect the anti-platelet activity of aspirin.

Efficacy

Introduction

Low-dose ASA is routinely prescribed for the secondary prevention of cardiac and cerebrovascular events. Continuous ASA use is associated with significant reductions in non-fatal re-infarction, non-fatal stroke and vascular death. It may also cause reduced rates of myocardial infarction when used for primary prevention. However, ASA is associated with an increased frequency of dyspeptic symptoms. Gastric or duodenal ulcers are found in up to 10% of users, although the majority of patients with peptic ulcers have no more symptoms than those without ulcers. Serious GI ulcer complications (mainly GI bleeding) occur in approximately 1% of patients per year taking low-dose ASA, two to four times more frequently than controls. Proton pump inhibitors (PPI) are widely recommended for the prevention and treatment of patients at high risk of peptic ulcer due to ASA[12] but no combination product is currently licenced.

An overview of the key clinical efficacy studies to support the use of a fixed combination of esomeprazole and ASA is shown in Table 5. Two Phase III efficacy studies (D9617C00011 and D961FC00003) were conducted to show that esomeprazole 20 mg and 40 mg once daily reduces the rate of gastric and duodenal ulcers in patients taking low-dose ASA at

[11] Andrew O. Maree, Ronan J. Curtin, Michelle Dooley, Ronan M, Conroy, Peter Crean, Dermot Cox, Desmond J. Fitzgerald. Platelet Response to Low-Dose Enteric-Coated Aspirin in Patients With Stable Cardiovascular Disease. J. Am Coll Cardiol. 2005: 45(7):1258-63.
[12] ACCF/ACG/AHA 2008 Expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. JACC (2008) Vol 52, No.18.

risk of developing peptic ulcers. Both were randomised, double-blind, 26 week studies performed in patients receiving E20, E40 or matching placebo on a background of continuous low-dose ASA prophylactic treatment.

Table 5. Study D9617C00011

Tal Summary of patient completion status, n(%)

Patient Completion Status	E20 (n=494)	Placebo (n=498)	Total (n=992)
Completed	425(86.0)	390(78.3)	815(82.2)
Discontinued	69(14.0)	108(21.7)	177(17.8)
Reason for discontinuation			
Eligibility criteria not fulfilled	7(1.4)	6(1.2)	13(1.3)
Adverse event	19(3.8)	26(5.2)	45(4.5)
Lack of therapeutic response	2(0.4)	26(5.2)	28(2.8)
Development of study specific discontinuation criteria	7(1.4)	8(1.6)	15(1.5)
Low dose ASA treatment permanently stopped	4(0.8)	5(1.0)	9(0.9)
Other	3(0.6)	3(0.6)	6(0.6)
Patient lost to follow-up	9(1.8)	3(0.6)	12(1.2)
Other	25(5.1)	39(7.8)	64(6.5)

E20 esomeprazole 20 mg od; ASA acetylsalicylic acid

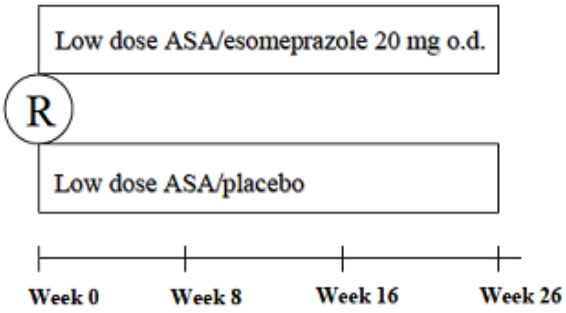
Main (pivotal) studies

Study D9617C00011 (ASTERIX) was a randomised, double-blind, placebo-controlled study to assess the prevention of low-dose acetylsalicylic acid (ASA) associated gastroduodenal lesions and upper gastrointestinal symptoms in patients taking esomeprazole 20 mg (E20) once daily (od) for 26 weeks.

Methods

The study schema is shown in Figure 2 below. A total of 78 sites in Australia, Europe, Canada, South Africa and Hong Kong recruited 992 patients. The trial was randomised, double-blind, two-armed, parallel group and placebo-controlled, studying the effects of E20 on gastroduodenal lesions, erosive oesophagitis and upper GI symptoms in patients taking low-dose ASA (75-325 mg daily). Efficacy, laboratory evaluations and adverse events (AE) were recorded at baseline, at 8, 16 and 26 weeks, and after additional visits if they were required. A physical examination with vital signs was completed at baseline and final visit. Helicobacter pylori (H. pylori) status was assessed at screening using local procedures, including serology, biopsy or other tests. A second analysis was performed at Visit 1 to confirm that patients were H. pylori negative, using the urea breath test (UBT) analysed at a central laboratory. These test results were not made available to the investigator until the patients had completed the study. Upper GI endoscopy was performed at baseline, 8 and 26 weeks or when a patient withdrew from the study before Week 26. Patients continued in the study until Week 26 unless endoscopy confirmed the presence of gastric or duodenal ulceration. Patients with gastric or duodenal ulceration were withdrawn from the study and treated with standard therapy at the discretion of the investigator.

Figure 2. Study Design



Objectives

The primary objective was to compare the effect of E20 once daily versus placebo for up to 26 weeks on the prevention of gastric and/or duodenal ulcers (a combined endpoint) in patients taking low-dose ASA.

The secondary objectives were, over a 26 week period, to compare the effect of E20 od versus placebo on the prevention of oesophageal lesions using the Los Angeles (LA) classification[13] in patients taking low-dose ASA; to compare investigator assessed symptoms (defined as none or mild symptoms) from the upper GI tract in patients treated with E20 or placebo who were receiving low-dose ASA; and to assess safety and tolerability of treatment with E20 od in patients taking low-dose ASA.

Study participants

Key inclusion criteria were males and females with the medical need (cardiovascular or cerebrovascular) for daily low-dose ASA for the duration of the study; age >60 years; no gastric or duodenal ulceration at baseline endoscopy; and no evidence of H. pylori infection by conventional testing.

Key exclusion criteria were upper GI symptoms requiring medical treatment; erosive oesophagitis; H. pylori infection; Zollinger-Ellison syndrome; other significant upper GI or pancreatic pathology; unstable diabetes; concomitant NSAIDs; recent unstable angina, myocardial infarction, transient ischaemic attack (TIA) or stroke; PPI or H2 antagonists 2 weeks before baseline; warfarin or other anticoagulant therapy with the exception of clopidogrel; steroids with an equivalent prednisolone dose >10 mg daily; a range of concomitant therapies with the potential to cause drug-drug interactions.

Treatments

Patients received clinical trial capsules containing esomeprazole 20 mg or matching placebo.

Treatment compliance and withdrawals

Patients were instructed to return containers and unused study medications at each visit for reconciliation. Discrepancies were discussed with the patients and the reasons noted

[13] None: No mucosal breaks
Grade A: One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds
Grade B: One (or more) mucosal break more than 5 mm that does not extend between the tops of two mucosal folds
Grade C: One (or more) mucosal break that is continuous between the tops of two mucosal folds but which involves less than 75% of the circumference
Grade D: One (or more) mucosal break which involves at least 75% of the oesophageal circumference

in the case report form (CRF). Antacid tablet rescue medication was provided with the investigational product and use of rescue medication was also monitored by tablet count at each study visit. Patients were withdrawn from the study for safety reasons; non-compliance; significant protocol violations; lack of efficacy with the development of gastric or duodenal ulceration; and permanent cessation of ASA therapy. Patients discontinued study treatment and discharged from the study if they developed an endoscopy proven ulcer before Visit 4. If withdrawal occurred between visits, an extra visit was scheduled with endoscopy, physical examination, AE assessment, laboratory tests, symptom assessment and drug accountability.

Outcomes/endpoints

The primary efficacy endpoint was the presence of gastric and/or duodenal ulceration at endoscopy in a 26 week period in patients taking low-dose ASA. Endoscopy of the oesophagus, stomach and duodenum was performed at baseline, 8 weeks and 26 weeks, or at premature discontinuation, or when clinically indicated. Secondary endpoints were LA classification of the oesophagus; upper GI symptoms assessed by the investigator at each visit; and AE, laboratory parameters and vital signs.

Sample size and statistics

The safety population included all patients who had taken at least one dose of study medication; the Intent to treat (ITT) population consisted of all randomised patients without gastric or duodenal ulceration at baseline; and the Per Protocol (PP) population consisted of all patients who met the inclusion and exclusion criteria. Primary and secondary endpoints were evaluated using the ITT population and the primary endpoint was also evaluated in the PP population. Statistical analysis was performed using SAS, Version 8.2. Kaplan-Meier life-table analyses were used for the primary endpoint until occurrence of gastric and/or duodenal ulceration during 26 weeks treatment. The log-rank test was used to analyse differences between the esomeprazole and placebo treatment groups. The proportion of patients with no symptoms was compared to the proportion of patients with at most mild symptoms using a Cochran-Mantel-Haenszel chi-square test, stratified according to baseline symptoms. Differences in LA classification were analysed using the Wilcoxon rank sum test. No corrections for multiple comparisons were made. Safety data were compared descriptively. A sample size of 960 patients (480 patients per group) was required to provide 90% power to detect a 6.5% difference in ulcer occurrence rates of 6.5% for the esomeprazole group and 13% for the placebo group. Ulcer and drop-out rates were based on three previously published studies sponsored by AstraZeneca.

Randomisation

Subjects were centrally randomised on the first visit day. They were randomised 1:1 to receive either esomeprazole 20 mg capsules or matching placebo.

Blinding

The subjects and investigators were blind to the randomisation schedule.

Results

Recruitment

A total of 1153 patients were enrolled and 992 patients were randomised at 78 sites in 10 countries and 815 patients completed the study. H. pylori infection and ulcers detected at baseline were the main reasons for patients failing to be randomised. There were 991 patient in the ITT group; 981 patients in the safety population; and 612 patients in the PP group. More patients in the E20 group completed the study than in the placebo group (86.0% versus 78.3%). The main reason for the difference was a greater discontinuation

rate in the placebo group. This was largely due to a relative lack of therapeutic response in the placebo group (5.2% for the placebo group and 0.4% for the E20 group).

Conduct of the study

Protocol deviations: Primary and secondary endpoints were based on the ITT population and the primary endpoint was also evaluated in the PP set. One patient in the E20 group was excluded from the ITT analysis because of a duodenal ulcer at baseline. Seven patients in the E20 group (1.4%) and four patients (0.8%) in the placebo group were excluded from the safety set because they had not received study medication or had no data recorded after dosing. Approximately 22.5% of patients were false negative for H.pylori infection based on the screening test results. They were subsequently assessed as H. pylori positive based on a positive or missing UBT. Overall, 38.3% of patients were excluded from the PP set, mainly due to positive or missing H. pylori status. However, the proportion of patients excluded was similar in both treatment groups. Exclusions due to poor study drug compliance were 6.4% in total, with similar proportions in each group. Exclusions due to inadequate ASA intake were only 1% overall.

Baseline data: Overall, the baseline characteristics were similar in both treatment groups and in both analysis sets. The median age in both groups was approximately 69 years and approximately 39% were >70 years. About 57% were male and the great majority were White (approximately 89%). Approximately 22.5% of patients in each group were H. pylori positive and were excluded from the PP analysis set. The mean (standard deviation (SD)) mg dose of prescribed ASA was 127.4 (65.0) in the E20 group (median 100, range 75-325) compared with 120.6 (56.9) in the placebo group (median 100, range 75-325).

Numbers analysed: Approximately 99% of patients received at least one dose of study treatment and were evaluable for safety. Almost 100% were evaluable for the ITT set in each group, and approximately 62% in each group were evaluable for the PP analysis.

Outcomes and estimation

Primary efficacy analysis: In the ITT population, there was a lower cumulative occurrence of gastric and/or duodenal ulcer (GU/DU) in the E20 group compared with the placebo group over the 26 week treatment period. The proportion of patients without GU/DU was 98.2% (95% CI: 96.9%-99.4%) in the E20 group and 93.8% (95% CI: 91.5%-96.1%) in the placebo group (p=0.0007). In the PP population, the proportion of patients without GU/DU was 98.3% (95% CI: 96.8%-99.8%) in the E20 group and 93.9% (95% CI: 91.1%-96.7%) in the placebo group (p=0.0067). During the 26 week treatment period, GU/DU occurred in 6.2% of placebo patients and 1.8% of the E20 patients, with a relative risk reduction of 70%. The PP analysis did not include patients who were H. pylori positive. The comparable efficacy results suggest that E20 has a similar effect in both H. pylori positive and negative patients.

Secondary efficacy variables:

LA classification of oesophagus: The cumulative occurrence of oesophageal lesions was significantly lower at 26 weeks in the E20 group (1.7%) compared with the placebo group (11.5%), p<0.0001. Of the patients who had lesions at baseline, 28.3% in the E20 group and 71.2% in the placebo group still had lesions after 26 weeks treatment.

Upper GI symptoms assessed by investigator: The absence of upper GI symptoms was assessed by the investigator at Months 2, 4 and 6. The great majority of patients had no upper GI symptoms at baseline. The occurrence of epigastric pain, epigastric burning, heartburn and acid regurgitation was significantly lower in the E20 group compared with the placebo group at Month 2 (Table 6). A similar response pattern was observed at Months 4 and 6 with varying levels of statistical significance.

Table 6. Study D9617C00011

Absence of investigator-assessed GI symptoms at Month 2 (ITT population)

Symptom	Baseline	E20 Absent	Placebo Absent
Epigastric pain	Absent	387/395(98.0%)	374/407(91.9%)
	Present	43/59(72.9%)	33/50(66.0%)
	All	430/454(94.7%)	407/457(89.1%)
	CMH[a] (versus placebo)	0.0005	
Epigastric burning	Absent	395/408(96.8%)	392/420(93.3%)
	Present	32/46(69.6%)	21/37(56.8%)
	All	427/454(94.1%)	413/457(90.4%)
	CMH[a] (versus placebo)	0.0109	
Epigastric discomfort	Absent	359/387(92.8%)	345/384(89.8%)
	Present	44/67(65.7%)	45/73(61.6%)
	All	403/454(88.8%)	390/457(85.3%)
	CMH[a] (versus placebo)	0.1629	
Heartburn	Absent	401/413(97.1%)	372/410(90.7%)
	Present	35/41(85.4%)	30/47(63.8%)
	All	436/454(96.0%)	402/457(88.0%)
	CMH[a] (versus placebo)	<0.0001	
Acid regurgitation	Absent	413/427(96.7%)	401/433(92.6%)
	Present	22/27(81.5%)	17/24(70.8%)
	All	435/454(95.8%)	418/457(91.5%)
	CMH[a] (versus placebo)	0.0051	
Nausea	Absent	409/424(96.5%)	423/440(96.1%)
	Present	25/30(83.3%)	8/17(47.1%)
	All	434/454(95.6%)	431/457(94.3%)
	CMH[a] (versus placebo)	0.1667	
Bloating	Absent	337/364(92.6%)	355/383(92.7%)
	Present	61/90(67.8%)	43/74(58.1%)
	All	398/454(87.7%)	398/457(87.1%)
	CMH[a] (versus placebo)	0.4720	

[a] CMH test stratified by baseline severity.
ITT intention-to-treat; E20 esomeprazole 20 mg od; CMH Cochran-Mantel-Haenszel chi square test

Table 7. Study D9617C00011

Antacid intake, mean number of tablets per day (ITT population)

	E20 (n=469)	Placebo (n=461)	Total (n=930)
Mean(SD)	0.2(0.4)	0.3(0.5)	0.3(0.4)
Median	0.0	0.1	0.1
Range	0.0-3.4	0.0-4.0	0.0-4.0

ITT intention-to-treat; E20 esomeprazole 20 mg od

Rescue medication: Patients were permitted to use antacid rescue medication of up to six tablets daily when needed. As shown in Table 7, the mean number of tablets taken per day was low and similar in the E20 and placebo groups.

Evaluator Comments: *The treatment groups were well balanced with similar demographics and baseline characteristics. The majority of patients were male and White and most had been taking low-dose ASA (median 100 mg) for at least 4 weeks prior to randomisation. Compliance was similar in both groups. A large proportion of patients were excluded from the PP analysis because they had H. pylori infection detected by UBT after the first visit However, the proportion in each treatment group was similar, efficacy rates were similar in H. pylori positive and negative patients, and there were no significant differences between the analyses of the ITT and PP population sets. The cumulative proportion of patients with GU/DU at 26 weeks was significantly lower in the E20 group (1.8%) than in the placebo group (6.2%) with a relative reduction in ulcer occurrence of 70%.*

Study D961FC00003 (OBERON) was a randomised, double-blind, parallel-group, multicentre, Phase 3 study to assess the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of peptic ulcers during 26 weeks in subjects on continuous low-dose acetylsalicylic acid (ASA).

Methods

The study was designed to compare the effect of esomeprazole 20 and 40 mg od on the occurrence of peptic ulcers in patients receiving continuous low-dose ASA (75-325 mg daily for at least 5 days per week for a 26 week treatment period). Treatment with low-dose ASA was instituted for primary or secondary prevention of cardiovascular or cerebrovascular thromboembolic events. Patients were required to be H. pylori negative at screening. H. pylori status was assessed at screening using local procedures, including serology, biopsy or other tests. A second analysis was performed at Visit 1 to confirm that patients were H. pylori negative, using the urea breath test (UBT) analysed at a central laboratory. These test results were not made available to the investigator until the patients had completed the study. The study plan was to randomise approximately 2400 male and female patients in about 20 countries. Upper GI endoscopy was performed at baseline and at 8 and 26 weeks; if the patient withdrew from the study; and if it was otherwise clinically indicated. The primary endpoint was the occurrence of peptic ulcer.

Secondary endpoints included the Reflux Disease Questionnaire (RDQ), a validated self-administered questionnaire for symptom evaluation containing 12 items answered on a six point scale based on severity. Four dimensions are assessed, namely regurgitation, heartburn, dyspepsia and gastro-oesophageal reflux disease (GORD). Symptoms were also assessed by the investigator using a four graded scale examining epigastric pain, epigastric burning, epigastric discomfort, heartburn, acid regurgitation, nausea, bloating, sleep disturbance and chest pain.

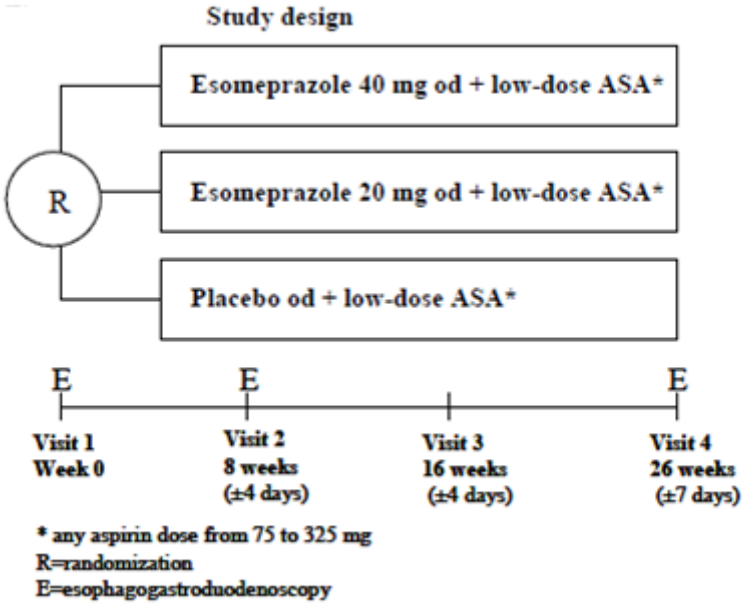
A medical and surgical history was taken at baseline and patient-reported upper GI symptoms were assessed by RDQ at each visit. A physical examination was performed at baseline and the final visit. In addition to randomised treatment, antacid rescue medication with an acid binding capacity of <16 mmol hydrochloric acid (HCl) was provided for upper GI symptoms considered intolerable by the patient.

The study design is summarised in the Figure 3 below.

Objectives

No drugs are currently approved for the prevention of peptic ulcers associated with the use of low-dose ASA for the prevention of thromboembolic events in at risk patients. However, previous studies have shown that esomeprazole reduced the incidence of peptic ulcers over 26 weeks in patients taking NSAIDs other than aspirin. The primary objective of this study was to compare the effects of E20 and E40 on the cumulative occurrence of GU/DU over a 26 week treatment period.

Figure 3. Study D961FC00003 design



Study participants

Key inclusion criteria included*:* physician initiated low-dose ASA (75-325 mg daily) expected to continue for the duration of the study; and H. pylori negative at screening. In addition, patients were required to fulfil at least one of the following criteria:

- Aged ≥65 years
- Aged ≥18 years with a documented history of uncomplicated peptic ulcer
- Aged ≥60 years and naïve to low-dose ASA
- Aged ≥60 years with stable coronary artery disease
- Aged ≥60 years with upper GI symptoms requiring an endoscopy and with the finding of at least five gastric or duodenal erosions.

Key exclusion criteria included: reflux oesophagitis grade C or D at baseline or within the previous year; peptic ulcer detected at baseline endoscopy; history of clinically significant peptic ulcer complications such as bleeding or perforation; previous gastric surgery; clinically significant vascular disease including unstable hypertension, unstable coronary artery disease, heart failure or recent stroke; clinically significant GI disease, pancreatitis or unstable diabetes; continuous NSAID therapy before randomisation; anticoagulant therapy; and any use of PPI or H_2-receptor antagonists immediately before randomisation.

Treatments

Patients received capsules containing esomeprazole 20 mg or 40 mg od or matching placebo.

Outcome/endpoints

The primary efficacy endpoint derived from endoscopy was the time to occurrence of peptic ulcer. Secondary endpoints were time to occurrence of GU; time to occurrence of DU; and the number of gastric and/or duodenal erosions. Other secondary endpoints were patient reported dyspeptic and GORD symptoms assessed by the RDQ; and upper GI assessment by the investigator.

Sample size and statistics

All patients who received at least one dose of study drug were included in the safety analysis. The ITT set included all patients without a peptic ulcer who were randomised at baseline; and the PP set included all patients randomised without major protocol inclusion/exclusion criteria violations. Primary and secondary endpoints were analysed in the ITT set and the primary endpoint was analysed in the PP set. The primary and secondary objectives measuring the occurrence of GU/DU were measured in a hierarchical closed test procedure. Each step of the procedure tested placebo versus E40 and placebo versus E20 and p values were adjusted according to the Hochberg procedure. The log rank test was used to assess differences between the esomeprazole groups and the placebo group. Low-dose ASA dose groups (75-100 mg and 101-325 mg) 12th were included as strata in the log rank test. Kaplan-Meier tables were used to illustrate time to occurrence of GU/DU for each group. Absolute and relative risk reduction of peptic ulcers were measured for each esomeprazole group compared with placebo with descriptive statistics used to present GU and DU occurrence. The Cochran Mantel-Haenszel chi-square test was used to measure the proportions of patients without any dyspeptic symptoms at last visit compared with baseline.

The sample size of 2400 (800 patients in each arm) was based on Study D9617C00011 reviewed above, which had with a higher placebo event rate of 8% assumingly because the study population was in a higher risk category. The relative risk reduction for peptic ulcer was assumed to be 60% which implied an event rate of 3.2% in the esomeprazole group. The relative risk reduction was assumed to be the same for GU and DU, implying an event rate for GU of 2.24% in the esomeprazole groups. The study had 90% power to detect a significant difference in the primary endpoint with a significance of 0.025 and a dropout rate of 15%.

Randomisation

Subjects were centrally randomised 1:1:1 to receive capsules containing esomeprazole 20 mg, esomeprazole 40 mg or placebo.

Blinding

The esomeprazole and placebo capsules were of identical appearance and they were packed and dispensed in identical bottles. The central randomisation code was kept by the sponsor although sealed individual codes were available to the investigator and pharmacist at each site in the event of medical emergency.

Treatment compliance and withdrawals

Patients were instructed to return containers and unused study medications (including rescue medication) at each visit for reconciliation. Patients were withdrawn from the study for safety reasons; non-compliance; significant protocol violations; lack of efficacy with the development of gastric or duodenal ulceration; and permanent cessation of ASA therapy. If withdrawal occurred between visits, an extra visit was scheduled with endoscopy, physical examination, AE assessment, laboratory tests, symptom assessment and drug accountability.

Results

Protocol deviations

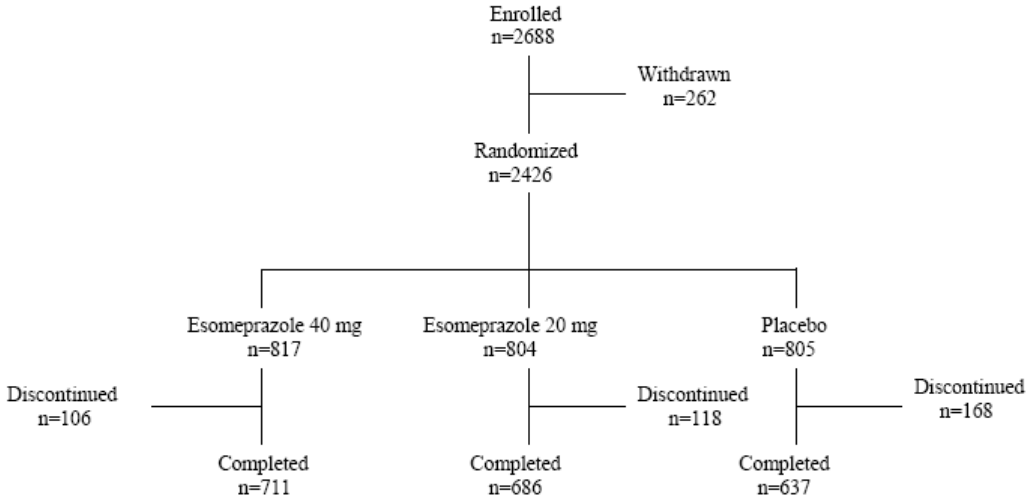
There was a similar frequency of significant protocol deviations in each group. Overall, 22.9% of patients randomised at screening were subsequently shown to be H. Pylori positive based on UBT (positive, not done or missing). Major deviations from the inclusion/exclusion criteria occurred in ≤4% in any treatment group. The mean dose of ASA was 110 mg and inadequate intake of ASA was reported in <0.5% of patients in any

group. Significant non-compliance with randomised treatment was 1.5% in patients receiving placebo compared with 1% overall.

Subject disposition

A total of 2688 patients were enrolled into the study and the numbers of completed and withdrawn patients are shown in Figure 4 below.

Figure 4. Subject disposition



Overall, 16.2% of patients discontinued the study. The discontinuation rate was higher in the placebo group (20.9%), due mainly to lack of therapeutic response. Withdrawals due to AE were 3.6% overall with a similar proportion in each group.

Baseline data

The study was conducted at 204 sites in 20 countries, including Argentina, Australia, Bulgaria, Canada, Czech Republic, Finland, Germany, Indonesia, Mexico, Norway, Philippines, Poland, Portugal, Romania, Russia, Slovakia, South Africa, South Korea, Thailand and USA.

Subject demographics were similar in each group. The median age was 67.6 years and approximately 36% were older than 75 years. Approximately 52.3% of patients were male and over 80% were White. More than 80% of patients had received regular ASA for at least 4 weeks before randomisation. More than 85% had no previous history of GU or DU and more than 90% had no history of erosive oesophagitis.

The endoscopic findings at baseline in the ITT population showed that approximately 10% of patients had duodenal erosions at baseline and 43% had gastric erosions. Findings in the PP set were exactly similar (data not shown). Approximately one third of patients experienced dyspeptic or GORD symptoms at baseline

Numbers analysed: Overall, 99.5% of patients were evaluable for safety. A total of 2426 (100%) patients were evaluable for the ITT set and 1534 (63.2%) were evaluable in the PP set. A total of 22.9% of patients in the ITT set were disallowed from the PP population because they were H. pylori positive or UBT was not done or missing.

Outcomes: The observed rates for the primary endpoint of GU/DU by Week 26 in the ITT set are shown in Table 8. The observed rates for the primary and secondary endpoints were comparable in the PP set.

Table 8. Study D961FC00003

Table 23 Cumulative proportion of subjects with peptic, gastric and duodenal ulcers by Week 26, ITT population

	Statistic	E40 n=817	E20 n=804	Placebo n=805
Primary variable: Peptic ulcers	Life table estimate	1.5%	1.1%	7.4%
	95% confidence intervals	0.6%-2.4%	0.3%-1.9%	5.5%-9.3%
	Observed response rate	11/817(1.3%)	8/804(1.0%)	53/805(6.6%)
	95% confidence intervals	0.7%-2.4%	0.4%-2.0%	5.0%-8.5%
	ARR (95% CI)	5.2%(3.4%-7.1%)	5.6%(3.7%-7.4%)	
	RRR	79.6	84.9	.
	Log rank p-value (vs Placebo)	<0.0001	<0.0001	.
	Statistical significance[a]	yes	yes	
Secondary variable: Gastric ulcers	Life table estimate	1.2%	0.8%	4.7%
	95% confidence intervals	0.4%-2.0%	0.2%-1.5%	3.1%-6.2%
	Observed response rate	9/817(1.1%)	6/804(0.7%)	33/805(4.1%)
	95% confidence intervals	0.5%-2.1%	0.3%-1.6%	2.8%-5.7%
	ARR (95% CI)	3.0%(1.5%-4.5%)	3.4%(1.9%-4.8%)	
	RRR	73.1	81.8	.
	Log rank p-value (vs Placebo)	<0.0001	<0.0001	.
	Statistical significance[a]	yes	yes	
Secondary variable: Duodenal ulcers	Life table estimate	0.3%	0.3%	3.1%
	95% confidence intervals	-0.1%-0.7%	-0.1%-0.6%	1.8%-4.4%
	Observed response rate	2/817(0.2%)	2/804(0.2%)	22/805(2.7%)
	95% confidence intervals	0.0%-0.9%	0.0%-0.9%	1.7%-4.1%
	ARR (95% CI)	2.5%(1.3%-3.7%)	2.5%(1.3%-3.7%)	
	RRR	91.0	90.9	.
	Log rank p-value (vs Placebo)	<0.0001	<0.0001	.
	Statistical significance[a]	yes	yes	

ITT=Intention To Treat; GU=Gastric Ulcer; DU=Duodenal ulcer;E40=esomeprazole 40 mg; E20=esomeprazole 20 mg; ARR=Absolute relative risk reduction;RRR=Relative risk reduction; CI=Confidence intervals
2 subjects in the placebo group had both gastric and duodenal ulcers and they are presented in the table for both variables.

[a] A hierarchical closed test procedure, done in parallel for the 2 different doses,with adjustment according to the Hochbergs procedure.

Due to the normal approximation used in the calculations of the CIs the lower CIs for E40 and E20 for duodenal ulcers become negative.

Peptic ulcers occurred in 11/817 [1.3% (95% CI: 0.7-2.4%)] patients in the E40 group, 8/804 [1.0% (95% CI: 0.4-2.0%)] in the E20 group, and 53/805 [6.6% (95% CI: 5.0-8.5%)] in the placebo group. The log rank p-value was <0.0001 for both esomeprazole groups compared with placebo. Absolute risk reduction (ARR) for peptic ulcer in the E40 group was 5.2% (95% CI: 3.4-7.1%) versus placebo and the relative risk reduction (RRR) was 79.6. ARR for peptic ulcer in the E20 group was 5.6% (95% CI: 3.7-7.4%) versus placebo and RRR was 84.9.

The observed rates for the secondary endpoint of GU were 9/817 [1.1% (95% CI: 0.5-2.1%)] in the E40 group, 6/804 [0.7% (95% CI: 0.3-1.6%)] in the E20 group and 33/805 [4.1% (95% CI: 2.8-5.7%)] in the placebo group (p<0.0001 for both esomeprazole groups versus placebo). ARR for GU in the E40 group was 3.0% (95% CI: 1.5-4.5%) versus placebo and RRR was 73.1. ARR for peptic ulcer in the E20 group was 3.4% (95% CI: 1.9-4.8%) versus placebo and RRR was 81.8.

Observed rates for the secondary endpoint of DU were 2/817 [0.2% (95% CI: 0.0-0.9%)] in the E40 group, 2/804 [0.2% (95% CI: 0.0-0.9%)] in the E20 group, and 22/805 [2.7% (95% CI: 1.7-4.1%)] in the placebo group. The log rank p-value was <0.0001 for both esomeprazole groups compared with placebo. ARR for DU in the E40 group was 2.5% (95% CI: 1.3-3.7%) versus placebo and RRR was 91.0. ARR for DU in the E20 group was 2.5% (95% CI: (1.3-3.7%) versus placebo and RRR was 90.9.

The cumulative proportions of patients with peptic ulcer described according to baseline characteristics showed that there were no obvious differences in any group but the event

numbers were too small to allow meaningful comparisons. The cumulative observed proportions of patients with peptic ulcer by ASA dose at Week 26 are showed that there were no clinically meaningful differences between the 75-100 mg and the 101-325 mg groups (1911 and 510 patients, respectively).

Dyspeptic and GORD symptoms were assessed by RDQ at Week 26. There were statistically significant reductions in symptoms in both esomeprazole groups as shown in Table 9.

Table 9. Study D961FC00003

Proportion of subjects without dyspeptic and GERD symptoms according to RDQ by Week 26,ITT population

Dimension	Baseline	E40 Absent	E20 Absent	Placebo Absent
Dyspeptic symptoms	Absent	372/415(89.6%)	371/417(89.0%)	335/412(81.3%)
	Present	219/367(59.7%)	206/341(60.4%)	169/351(48.1%)
	CMH (vs placebo)	<0.0001	<0.0001	
GERD symptoms	Absent	303/350(86.6%)	292/342(85.4%)	264/337(78.3%)
	Present	251/432(58.1%)	245/416(58.9%)	187/426(43.9%)
	CMH (vs placebo)	<0.0001	<0.0001	

ITT=Intention To Treat; E40=esomeprazole 40 mg; E20=esomeprazole 20 mg; RDQ=Reflux Disease Questionnaire; CMH=Cochran Mantel Haenzel chi square test

The proportions of patients with gastric and/or duodenal erosions are shown in Table 10. The number of gastric and duodenal erosions by Week 26 was lower in both esomeprazole groups compared with placebo. Upper GI symptoms assessed by the investigator are summarised in Table 11. Symptoms were reported less frequently at Week 26 in the esomeprazole groups compared with placebo and the findings were similar to those assessed by RDQ. The cumulative proportions of patients with signs of clinically significant GI complications are shown in Table 12. There was one case of haematemesis with perforation in the E20 group and there were two cases of melaena in the placebo group. There were seven cases of haematochezia in the E40 group and three cases in the E20 group, all assumed to have arisen from the lower GI tract in the absence of other evidence. Complications reported as 'Other', such as pancreatitis, constipation and diarrhoea were assessed by the investigator as not associated with peptic ulcer.

Table 10. Study D961FC00003

Cumulative observed proportion of patients with erosions at baseline and by Week 26[a], ITT population

		E40 n=817		E20 n=804		Placebo n=805	
		baseline	26 weeks	baseline	26 weeks	baseline	26 weeks
Duodenal erosions	0	676(82.7%)	731(89.5%)	667(83.0%)	717(89.2%)	675(83.9%)	658(81.7%)
	1-4	54(6.6%)	31(3.8%)	59(7.3%)	26(3.2%)	52(6.5%)	58(7.2%)
	5-10	38(4.7%)	7(0.9%)	22(2.7%)	5(0.6%)	18(2.2%)	29(3.6%)
	>10	6(0.7%)	3(0.4%)	5(0.6%)	2(0.2%)	6(0.7%)	3(0.4%)
	Missing	43(5.3%)	45(5.5%)	51(6.3%)	54(6.7%)	54(6.7%)	57(7.1%)
Gastric erosions	0	436(53.4%)	565(69.2%)	414(51.5%)	552(68.7%)	433(53.8%)	389(48.3%)
	1-4	127(15.5%)	133(16.3%)	131(16.3%)	118(14.7%)	122(15.2%)	181(22.5%)
	5-10	157(19.2%)	58(7.1%)	150(18.7%)	59(7.3%)	141(17.5%)	110(13.7%)
	>10	54(6.6%)	16(2.0%)	57(7.1%)	21(2.6%)	55(6.8%)	68(8.4%)
	Missing	43(5.3%)	45(5.5%)	52(6.5%)	54(6.7%)	54(6.7%)	57(7.1%)
Total[b]	0	410(50.2%)	558(68.3%)	395(49.1%)	540(67.2%)	411(51.1%)	368(45.7%)
	1-4	129(15.8%)	131(16.0%)	133(16.5%)	124(15.4%)	125(15.5%)	180(22.4%)
	5-10	163(20.0%)	56(6.9%)	149(18.5%)	62(7.7%)	152(18.9%)	120(14.9%)
	>10	72(8.8%)	27(3.3%)	75(9.3%)	24(3.0%)	63(7.8%)	80(9.9%)
	Missing	43(5.3%)	45(5.5%)	52(6.5%)	54(6.7%)	54(6.7%)	57(7.1%)

ITT=Intention To Treat;E40=esomeprazole 40 mg; E20=esomeprazole 20 mg

[a] Max no of erosions assessed at a visit after baseline

[b] Gastric and/or duodenal erosions

D961FC00003_C00052

Table 11. Study D961FC00003

Absence of GI symptoms assessed by the investigator by 26 weeks, ITT population

GI symptom	Baseline	Absence of GI symptoms by 26 weeks		
		E40	E20	Placebo
Epigastric pain	Absent	477/524(91.0%)	458/505(90.7%)	454/520(87.3%)
	Present	187/268(69.8%)	187/267(70.0%)	158/255(62.0%)
Epigastric burning	Absent	487/536(90.9%)	496/533(93.1%)	465/537(86.6%)
	Present	196/256(76.6%)	170/239(71.1%)	143/238(60.1%)
Epigastric discomfort	Absent	447/487(91.8%)	437/481(90.9%)	437/498(87.8%)
	Present	204/305(66.9%)	213/291(73.2%)	151/277(54.5%)
Heartburn	Absent	482/518(93.1%)	472/510(92.5%)	433/513(84.4%)
	Present	208/274(75.9%)	200/262(76.3%)	169/262(64.5%)
Acid regurgitation	Absent	497/533(93.2%)	492/535(92.0%)	467/547(85.4%)
	Present	194/259(74.9%)	178/237(75.1%)	139/228(61.0%)
Nausea	Absent	639/676(94.5%)	623/658(94.7%)	639/674(94.8%)
	Present	84/116(72.4%)	94/114(82.5%)	72/101(71.3%)
Bloating	Absent	524/567(92.4%)	506/554(91.3%)	497/558(89.1%)
	Present	150/225(66.7%)	148/218(67.9%)	134/217(61.8%)
Sleep disturbance	Absent	594/643(92.4%)	591/631(93.7%)	569/627(90.7%)
	Present	100/149(67.1%)	87/141(61.7%)	87/148(58.8%)
Chest pain	Absent	628/658(95.4%)	608/645(94.3%)	599/642(93.3%)
	Present	98/134(73.1%)	100/127(78.7%)	93/133(69.9%)

ITT=Intention To Treat; E20=esomeprazole 20 mg; E40=esomeprazole 40 mg; GI=Gastro intestinal
Only patients with both assessments at baseline and after baseline
D961FC00003_C0042

Table 12. Study D961FC00003

Cumulative proportion of subjets with upper GI complications by Week 26, ITT population

Type of complicaction	E40	E20	Placebo
Haematemesis	0/790(0.0%)	1/771(0.1%)	0/770(0.0%)
Melaena	0/790(0.0%)	0/771(0.0%)	2/770(0.3%)
Haematochezia	4/790(0.5%)	3/771(0.4%)	0/770(0.0%)
Perforation	0/790(0.0%)	1/771(0.1%)	0/770(0.0%)
Gastric outlet obstruction	0/790(0.0%)	0/771(0.0%)	0/770(0.0%)
Other	14/790(1.8%)	13/771(1.7%)	20/770(2.6%)

ITT=Intention To Treat;E40=esomeprazole 40 mg; E20=esomeprazole 20 mg
Only subjects with assessment of upper GI complications are presented

Summary of efficacy

For patients taking daily ASA, E40 and E20 were more effective than placebo in preventing the occurrence of peptic ulcer, gastric ulcer and duodenal ulcer over a 26 week treatment period. Dyspeptic and GORD symptoms assessed by RDQ occurred less frequently in patients treated with E40 and E20 compared with placebo. Upper GI erosions occurred less frequently in patients taking E40 and E20 compared with placebo. Upper GI complications occurred infrequently in all treatment groups and the numbers were too small for meaningful comparison.

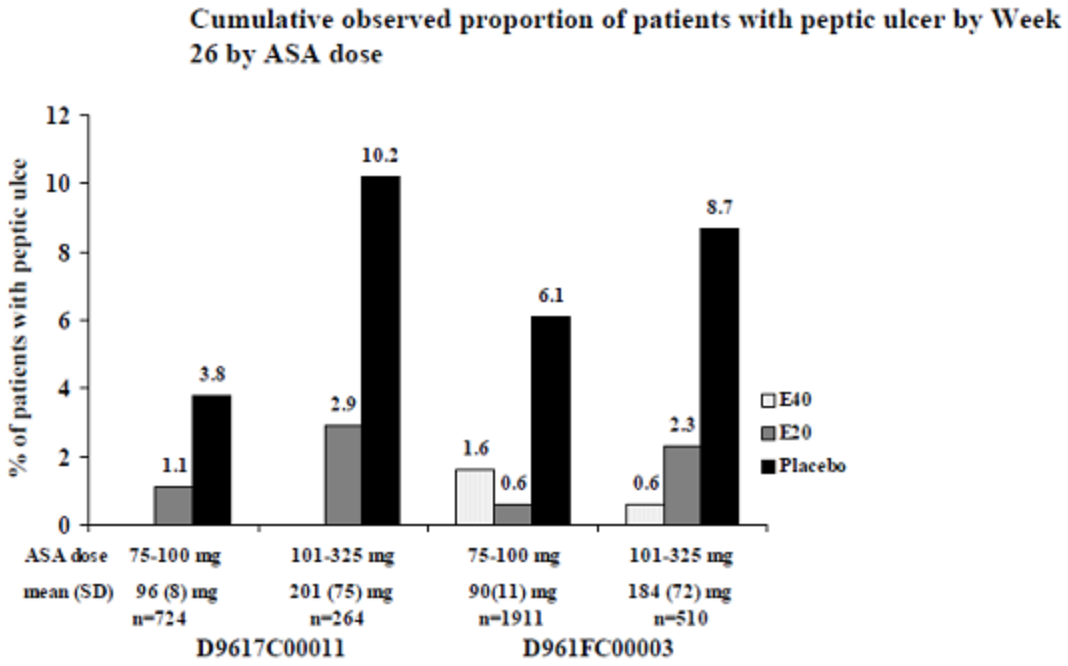
Evaluator Comment: *Efficacy for E20 and E40 was broadly similar and both were more effective than placebo for the prevention of peptic ulcer and upper GI symptoms. A large proportion of patients were excluded from the PP analysis because they had H. pylori infection. However, the proportion in each treatment group was similar and efficacy rates were similar in H. pylori positive and negative patients. There was no evidence to support the use of the higher esomeprazole dose.*

Clinical studies in special populations:

No studies were performed in special populations but the occurrence of peptic ulcers in sub-groups was compared in both Phase II studies. The occurrence of peptic ulcers was similar across sub-groups defined by gender, age, H. pylori status and ASA dose. The

majority of patients were White so no racial comparisons can be made. The occurrence of peptic ulcer in patients with and without H. pylori infection was lower in the esomeprazole groups compared with placebo. The outcome rates were similar in the ITT and PP analyses confirming the efficacy of esomeprazole in patients with and without H. pylori infection. Ulcer rates were higher in patients receiving higher ASA doses although approximately 75% of patients were using ASA doses in the range 75-100 mg. Esomeprazole was equally effective at reducing ulcer occurrence in the lower and higher ASA dose ranges as shown in Figure 5.

Figure 5



Analysis performed across trials (pooled analyses and meta-analysis)

Two Phase III studies were performed to support the application with 991 evaluable patients in D9617C00011 and 2426 patients in D961F00003. The baseline demographics in each study were similar; the majority of patients were male and Caucasian with a mean age of 68 years (approximately 35-40% of patients were aged 70 years or more). Over 20% of patients in each study were H. pylori positive. The average ASA doses in each study were 110 mg and 124 mg daily. The most commonly represented risk factors for peptic ulcer in each group were age ≥65 years and age ≥60 years with stable coronary artery disease. Withdrawal rates were approximately 5% higher in the placebo groups than in the active treatment groups. This difference was mainly due to lack of efficacy in the placebo group.

The primary efficacy endpoint was peptic ulcer in both studies. All endoscopists were trained in procedures and evaluation criteria to ensure that findings were recorded in a consistent manner. H. pylori status was assessed at the screening visit by serology and biopsy. UBT testing was performed at a central laboratory at Visit 1 and the result of the UBT was used to report baseline status. The investigator remained blind to the UBT results and patients with positive results were ultimately excluded from the PP analysis. Symptoms of dyspepsia and GORD, reported by patient-assessed RDQ or by the investigator, were consistent with the endoscopic findings in both studies. Peptic ulcer rates compared by baseline characteristics are shown in Table 13. Ulcer rates were broadly similar in all groups but they occurred more frequently in patients receiving higher doses of ASA. There were highly significant RRR for peptic ulcer in the esomeprazole groups compared with the placebo groups, ranging from 70.1% to 84.9%.

The differences in ARR in favour of the esomeprazole groups were much more modest, ranging from 3.8% (CI: 1.5%-6.1%) in Study D9617C00011 to 5.2% (CI: 3.4%-7.1%) and 5.6% (CI: 3.7%-7.4%) in Study D961FC00003. For gastric ulcer, the ARR in favour of esomeprazole was 2.6% in study D9617C00011 and 3.0% to 3.4% for in Study D961FC00003. For duodenal ulcer, the ARR in favour of E20 was 1.2% (CI: -0.0%-2.4%) in Study D9617C00011, and 2.5% (CI: 1.3%-3.7%) in the E20 and E40 arms of Study D961FC00003.

Table 13.

Table 2 Cumulative proportion of patients with peptic, gastric and duodenal ulcers by Week 26, ITT population

	Statistic	D9617C00011		D961FC00003		
		E20 n=493	Placebo n=498	E40 n=817	E20 n=804	Placebo n=805
Peptic ulcers	Life table estimate	1.8%	6.2%	1.5%	1.1%	7.4%
	95% confidence intervals	0.6%-3.1%	3.9%-8.5%	0.6%-2.4%	0.3%-1.9%	5.5%-9.3%
	Observed response rate	8/493(1.6%)	27/498(5.4%)	11/817(1.3%)	8/804(1.0%)	53/805(6.6%)
	95% confidence intervals	0.7%-3.2%	3.6%-7.8%	0.7%-2.4%	0.4%-2.0%	5.0%-8.5%
	ARR (95% CI)	3.8%(1.5%-6.1%)		5.2%(3.4%-7.1%)	5.6%(3.7%-7.4%)	
	RRR	70.1	.	79.6	84.9	.
	Log rank p-value (vs placebo)[b]	0.0005	.	<0.0001	<0.0001	.
	Statistical significance[a]	yes		yes	yes	
Gastric ulcers	Life table estimate	1.4%	4.5%	1.2%	0.8%	4.7%
	95% confidence intervals	0.3%-2.5%	2.5%-6.5%	0.4%-2.0%	0.2%-1.5%	3.1%-6.2%
	Observed response rate	6/493(1.2%)	19/498(3.8%)	9/817(1.1%)	6/804(0.7%)	33/805(4.1%)
	95% confidence intervals	0.4%-2.6%	2.3%-5.9%	0.5%-2.1%	0.3%-1.6%	2.8%-5.7%
	ARR (95% CI)	2.6%(0.7%-4.5%)		3.0%(1.5%-4.5%)	3.4%(1.9%-4.8%)	
	RRR	68.1	.	73.1	81.8	.
	Log rank p-value (vs placebo)[b]	0.0046	.	<0.0001	<0.0001	.
	Statistical significance[a]	yes		yes	yes	
Duodenal ulcers	Life table estimate	0.5%	1.8%	0.3%	0.3%	3.1%
	95% confidence intervals	-0.2%-1.1%	0.6%-3.1%	-0.1%-0.7%	-0.1%-0.6%	1.8%-4.4%
	Observed response rate	2/493(0.4%)	8/498(1.6%)	2/817(0.2%)	2/804(0.2%)	22/805(2.7%)
	95% confidence intervals	0.0%-1.5%	0.7%-3.1%	0.0%-0.9%	0.0%-0.9%	1.7%-4.1%
	ARR (95% CI)	1.2%(-0.0%-2.4%)		2.5%(1.3%-3.7%)	2.5%(1.3%-3.7%)	
	RRR	74.7	.	91.0	90.9	.
	Log rank p-value (vs placebo)[b]	0.0431	.	<0.0001	<0.0001	.
	Statistical significance[a]	yes		yes	yes	

ITT intention to treat; E40 esomeprazole 40 mg od; E20 esomeprazole 20 mg od; ARR absolute risk reduction; RRR relative risk reduction; CI confidence intervals.

[a] A hierarchical closed test procedure, done in parallel for the 2 different doses(D961FC00003 only), with adjustment according to Hochbergs procedure.

[b] Log-rank test stratified by ASA dose (75-100 mg and 101-325 mg daily). The prespecified analysis according to the CSP without stratification for study D9617C00011 is presented in the CSR.

Due to the normal approximation used in the calculation of the CIs, the lower CIs for duodenal ulcer become negative for esomeprazole 20 and 40 mg.

2 subjects in Study D961FC00003 had both gastric and duodenal ulcers and they are presented in the table for both variables.

Supportive studies

None submitted.

Evaluator's overall conclusions on clinical efficacy

Both doses of esomeprazole reduced the incidence of peptic ulcer, gastric ulcer and duodenal ulcer after 26 weeks treatment. In Study D961FC00003, the Kaplan-Meier estimates for peptic ulcer were 1.5% and 1.1% in the esomeprazole groups compared with 7.4% in the placebo group, a relative risk reduction of 80-85%. In Study D9617C00011, the estimates were 1.8% in the esomeprazole group compared with 6.2% in the placebo group, a relative risk reduction of 70%. Similar response rates were observed for other endoscopic findings including gastric and duodenal erosions. Patient-reported symptoms measured by RDQ and investigator-assessed symptoms were also consistently reduced in the esomeprazole groups compared with placebo. The relative frequencies of complications of peptic ulceration were not a predetermined protocol criterion. Event numbers were small in both studies but presumed upper GI bleeding was more frequent in the placebo group than in the esomeprazole groups (discussed further in the Safety review below).

Safety

Introduction

From data supplied by AstraZeneca, over 1140 million courses of esomeprazole have been delivered to wholesalers worldwide and more than 89,000 patients have been exposed in clinical trials. Commonly reported adverse events include headache, diarrhoea, constipation, flatulence, nausea, vomiting and abdominal pain. Most adverse events are considered to be mild and reversible and no specific events of interest were flagged prospectively in the two Phase III studies. Some adult patients are intolerant or allergic to aspirin but adverse events related to low-dose aspirin are almost exclusively GI related. The adverse event profiles of esomeprazole and low-dose ASA are well understood so no special safety monitoring was employed in either study. No adjudicating procedures were used to evaluate any safety endpoints, including ulcer complications or death. AE related to dyspepsia and GORD were captured as efficacy endpoint by RDQ and investigator assessment and were not included in the safety analysis.

All patients who received at least one dose of study medication were included in the safety population. Adverse events were classified using MedDRA terminology. Data for the Phase III studies were analysed as pooled data, individual studies and treatment arms. The E40 arm of Study D961FC00003 was not included in the pooled data. Pooled data were used to explore the effects of gender, age and race.

Patient exposure

A total of 104 healthy subjects were evaluated for safety in the Phase I studies. A total of 3395 patients were included in the Phase III study safety set; 814 received E40, 1286 received E20 and 1295 received placebo for a planned duration of 26 weeks. The median exposure was 181 days in all treatment arms. Patients in whom an ulcer was detected were required to be withdrawn so mean exposure was less in the placebo groups compared with the E40 and E20 groups. The baseline characteristics of the Phase III study safety population showed that there were more male than female patients and approximately 70% were ≥65 years of age. The majority of patients were White.

Adverse events

A summary of pooled adverse event rate data for the Phase III studies is shown in Table 14 and in Table 15 presented by study and treatment arm. Non-serious AE rates were similar in the active treatment and placebo groups. The most commonly reported AE were diarrhoea and upper respiratory tract infection. A summary of the AE reported in the pooled Phase III studies is shown in Table 16. The pattern of AE reported by individual study and treatment arms was similar to that of the pooled data. In general, the frequencies of AE were similar in the treatment groups and consistent with the known safety profile of esomeprazole. Table 17 summarises the most common AE data in the pooled population. In general, the differences in frequency between the E20 and placebo groups were unremarkable. The frequencies of cardiac and nervous system AE were marginally lower in the esomeprazole groups compared with placebo.

Table 14.

Number (%) of patients who had an AE in any category, safety population (pooled data from Study D9617C00011 and Study D961FC00003)

	Number(%) patients who had an AE in each category[a]	
AE Category	E20 n=1286	Placebo n=1295
Any AE	501(39.0%)	510(39.4%)
Fatal SAE	4(0.3%)	3(0.2%)
Non-fatal SAE	71(5.5%)	72(5.6%)
AE leading to discontinuation of treatment[b]	55(4.3%)	78(6.0%)
Related AEs[c]	53(4.1%)	49(3.8%)

E20 esomeprazole 20 mg od.

D9617C00011/E0075008 had AE (PT:Angina Pectoris) not included in the CSR. Presented here, as appearance on treatment could not be excluded.

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Investigational product permanently stopped due to adverse event.

[c] Related AEs are those for which there was a possible relationship to investigational product as judged by the investigator.

Table 15.

Number (%) of patients who had an AE in any category[a], safety population

	D9617C00011		D961FC00003		
AE Category	E20 n=487	Placebo n=494	E40 n=814	E20 n=799	Placebo n=801
Any AE	204(41.9%)	212(42.9%)	295(36.2%)	297(37.2%)	298(37.2%)
Fatal SAE	0(0.0%)	2(0.4%)	4(0.5%)	4(0.5%)	1(0.1%)
Non-fatal SAE	32(6.6%)	37(7.5%)	43(5.3%)	39(4.9%)	35(4.4%)
AE leading to discontinuation of treatment[b]	18(3.7%)	36(7.3%)	30(3.7%)	37(4.6%)	42(5.2%)
Related AEs[c]	14(2.9%)	18(3.6%)	34(4.2%)	39(4.9%)	31(3.9%)

E20 esomeprazole 20 mg od.

D9617C00011/E0075008 had AE (PT:Angina Pectoris) not included in the CSR. Presented here, as appearance on treatment could not be excluded.

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Investigational product permanently stopped due to adverse event.

[c] Related AEs are those for which there was a possible relationship to investigational product as judged by the investigator.

Table 16.

Adverse events by System Organ Class, N (%) of patients with adverse events, safety population (pooled data from Study D9617C00011 and Study D961FC00003)

System organ class	E20 n=1286	Placebo n=1295
Infections and infestations	179(13.9%)	178(13.7%)
Gastrointestinal disorders	153(11.9%)	143(11.0%)
Musculoskeletal and connective tissue disorders	68(5.3%)	81(6.3%)
Nervous system disorders	68(5.3%)	75(5.8%)
Cardiac disorders	35(2.7%)	41(3.2%)
Injury, poisoning and procedural complications	41(3.2%)	34(2.6%)
Respiratory, thoracic and mediastinal disorders	37(2.9%)	40(3.1%)
General disorders and administration site conditions	34(2.6%)	29(2.2%)
Skin and subcutaneous tissue disorders	34(2.6%)	26(2.0%)
Vascular disorders	27(2.1%)	25(1.9%)
Investigations	9(0.7%)	19(1.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18(1.4%)	15(1.2%)
Eye disorders	17(1.3%)	13(1.0%)
Metabolism and nutrition disorders	16(1.2%)	17(1.3%)
Renal and urinary disorders	17(1.3%)	10(0.8%)
Psychiatric disorders	14(1.1%)	16(1.2%)
Ear and labyrinth disorders	13(1.0%)	13(1.0%)
Reproductive system and breast disorders	10(0.8%)	9(0.7%)
Blood and lymphatic system disorders	9(0.7%)	6(0.5%)
Hepatobiliary disorders	8(0.6%)	3(0.2%)
Endocrine disorders	6(0.5%)	3(0.2%)
Immune system disorders	1(0.1%)	5(0.4%)
Congenital, familial and genetic disorders	1(0.1%)	0(0%)
Surgical and medical procedures	0(0%)	1(0.1%)

E20 esomeprazole 20 mg od.
D9617C00011/E0075008 had AE (PT:Angina Pectoris SOC:Cardiac disorders) not included in the CSR. Presented here, as appearance on treatment could not be excluded.

Table 17.

Number of patients with the most commonly reported adverse events in decreasing order of frequency, safety population (pooled data from Study D9617C00011 and Study D961FC00003)

Preferred term	E20 n=1286	Placebo n=1295
Diarrhoea	37(2.9%)	24(1.9%)
Upper respiratory tract infection	25(1.9%)	28(2.2%)
Nasopharyngitis	27(2.1%)	18(1.4%)
Bronchitis	26(2.0%)	23(1.8%)
Headache	20(1.6%)	26(2.0%)
Abdominal pain upper	9(0.7%)	23(1.8%)
Constipation	20(1.6%)	22(1.7%)
Dizziness	17(1.3%)	21(1.6%)
Dyspepsia	6(0.5%)	21(1.6%)
Back pain	18(1.4%)	19(1.5%)
Influenza	16(1.2%)	18(1.4%)
Urinary tract infection	18(1.4%)	15(1.2%)
Nausea	16(1.2%)	17(1.3%)
Hypertension	13(1.0%)	10(0.8%)
Pain in extremity	8(0.6%)	13(1.0%)

E20 esomeprazole 20 mg od.
A cut off of 1% has been used.

In Study D961FC00011, there were six withdrawals from the study because of bleeding complications; four patients in the placebo group and two patients in the E20 group. In Study D9617C00003, there were two withdrawals for upper GI complications in the E20 group (one haematemesis and one perforation, and two in the placebo group (both melaena). Haematochezia (bleeding assumed to originate in the lower GI tract) occurred in seven patients (four receiving E40 and three receiving E20).

Serious adverse events and deaths

There were no deaths in the Phase I studies. Deaths in the Phase III studies are described below. There were seven deaths in the pooled group; 4 (0.3%) in the E20 group and 3 (0.2%) in the placebo group. There were 11 deaths in the overall safety population. In Study D9617C00011, there were no deaths in the E20 group while two deaths occurred in the placebo group: one died of ischaemic stroke and the other died of bladder cancer. In Study D961F00003, nine patients died during the study: 4 (0.5%) in the E40 group, 4 (0.5%) in the E20 group and 1 (0.1%) in the placebo group. Five of these deaths appeared to be cardiac: two in the E40 group (myocardial infarction (MI) and sudden death), two in the E20 group (acute coronary syndrome (ACS)/cerebral circulatory failure and cardiac arrest), and one in the placebo group (MI). None of the deaths was considered to be causally related to study drug by the investigators. All deaths in Study D961F00003 occurred in patients at high risk of cardiovascular events: 7 patients had a past history of cardiovascular events and 2 patients had a history of diabetes and hypertension. Four patients died suddenly without a confirmed diagnosis or autopsy.

No serious AEs (SAEs) were reported in the Phase I studies during the treatment phase. Non-fatal SAE during the Phase III studies on pooled data are shown in Table 18 and on the safety population in Table 19. The frequencies of SAE were similar across treatment groups although nervous system disorders were slightly more common in the esomeprazole groups compared with placebo. Cerebrovascular disorders including cerebral arteriosclerosis, cerebral circulatory failure, cerebral infarction, cerebrovascular accident, cerebrovascular disorder, cerebrovascular insufficiency, ischaemic stroke, transient ischaemic attack and vascular encephalopathy occurred in 10 (0.5%) patients treated with esomeprazole and 2 (0.2%) patients during placebo treatment. However, when analysing all AE (deaths, SAE and AE) using the same preferred terms, 11 (0.5%) patients were in the esomeprazole groups and 7 (0.5%) patients were in the placebo group.

Table 18.

Serious adverse events other than deaths by System Organ Class, N (%) of patients with adverse events, safety population (pooled data from Study D9617C00011 and Study D961FC00003)

System organ class	E20 n=1286	Placebo n=1295
Cardiac disorders	15(1.2%)	20(1.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11(0.9%)	13(1.0%)
Nervous system disorders	13(1.0%)	6(0.5%)
Injury, poisoning and procedural complications	1(0.1%)	10(0.8%)
Gastrointestinal disorders	8(0.6%)	7(0.5%)
Infections and infestations	5(0.4%)	8(0.6%)
Musculoskeletal and connective tissue disorders	1(0.1%)	5(0.4%)
Respiratory, thoracic and mediastinal disorders	5(0.4%)	3(0.2%)
General disorders and administration site conditions	4(0.3%)	1(0.1%)
Hepatobiliary disorders	4(0.3%)	2(0.2%)
Eye disorders	2(0.2%)	0(0%)
Metabolism and nutrition disorders	3(0.2%)	0(0%)
Vascular disorders	1(0.1%)	3(0.2%)
Ear and labyrinth disorders	1(0.1%)	0(0%)
Endocrine disorders	0(0%)	1(0.1%)
Investigations	0(0%)	1(0.1%)
Psychiatric disorders	1(0.1%)	1(0.1%)
Reproductive system and breast disorders	0(0%)	1(0.1%)
Skin and subcutaneous tissue disorders	1(0.1%)	0(0%)
Renal and urinary disorders	0(0%)	0(0%)

E20 esomeprazole 20 mg od.
Patients reporting at least 1 SAE after first dose of investigational product.

Table 19.

Serious adverse events other than deaths by System Organ Class, N (%) of patients with adverse events, safety population

	D9617C00011		D961FC00003		
System organ class	E20 n=487	Placebo n=494	E40 n=814	E20 n=799	Placebo n=801
Cardiac disorders	8(1.6%)	14(2.8%)	9(1.1%)	7(0.9%)	6(0.7%)
Gastrointestinal disorders	1(0.2%)	3(0.6%)	13(1.6%)	7(0.9%)	4(0.5%)
Infections and infestations	3(0.6%)	6(1.2%)	4(0.5%)	2(0.3%)	2(0.2%)
Injury, poisoning and procedural complications	1(0.2%)	6(1.2%)	3(0.4%)	0(0%)	4(0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6(1.2%)	5(1.0%)	6(0.7%)	5(0.6%)	8(1.0%)
Nervous system disorders	6(1.2%)	3(0.6%)	2(0.2%)	7(0.9%)	3(0.4%)
Respiratory, thoracic and mediastinal disorders	2(0.4%)	3(0.6%)	1(0.1%)	3(0.4%)	0(0%)
Eye disorders	2(0.4%)	0(0%)	0(0%)	0(0%)	0(0%)
General disorders and administration site conditions	2(0.4%)	0(0%)	1(0.1%)	2(0.3%)	1(0.1%)
Hepatobiliary disorders	1(0.2%)	1(0.2%)	1(0.1%)	3(0.4%)	1(0.1%)
Metabolism and nutrition disorders	0(0%)	0(0%)	1(0.1%)	3(0.4%)	0(0%)
Musculoskeletal and connective tissue disorders	0(0%)	2(0.4%)	2(0.2%)	1(0.1%)	3(0.4%)
Vascular disorders	1(0.2%)	1(0.2%)	3(0.4%)	0(0%)	2(0.2%)
Investigations	0(0%)	1(0.2%)	0(0%)	0(0%)	0(0%)
Psychiatric disorders	1(0.2%)	1(0.2%)	0(0%)	0(0%)	0(0%)
Reproductive system and breast disorders	0(0%)	1(0.2%)	1(0.1%)	0(0%)	0(0%)
Ear and labyrinth disorders	0(0%)	0(0%)	0(0%)	1(0.1%)	0(0%)
Endocrine disorders	0(0%)	0(0%)	0(0%)	0(0%)	1(0.1%)
Renal and urinary disorders	0(0%)	0(0%)	1(0.1%)	0(0%)	0(0%)
Skin and subcutaneous tissue disorders	0(0%)	0(0%)	0(0%)	1(0.1%)	0(0%)

E20 esomeprazole 20 mg od.
Patients reporting at least 1 SAE after first dose of investigational product.

Laboratory findings

In the Phase I studies, there were no clinically significant laboratory abnormalities or laboratory AE. There were no clinically important differences between groups and the numbers of patients with values outside the reference ranges were also similar between groups.

With respect to mean changes in clinical chemistry values from baseline to last visit, there were slight increases in ALP in the esomeprazole groups but not in the placebo group during treatment. Changes in other laboratory values during the studies were otherwise minor and of no clinical significance.

Vital signs and electrocardiogram (ECG) abnormalities

Vital signs (blood pressure and heart rate) and ECGs were recorded at baseline and last visit and clinically significant changes were recorded as AE. The frequency of clinically significant changes was low (<1%) in each group. There was one SAE of severe hypertension in the placebo group of Study D9617C00011.

Safety in special populations

There were minor gender differences in the frequencies and discontinuations due to AE but none was clinically significant. A summary of AE reported by age showed that the frequency of AE was slightly higher in patients ≥65 years of age compared with those <65

years of age in both esomeprazole and placebo groups. However, the pattern of AE reported in the different age and treatment groups was similar.

Blacks appeared to have a lower frequency of AE compared with Whites and Orientals but the number of Blacks enrolled in the Phase III studies was small. There were no clinical relevant differences in haematology or clinical chemistry values regardless of gender, age or race.

Immunological events

Not applicable.

Safety related to drug-drug interactions and other interactions

No drug-drug interactions between esomeprazole and ASA have been identified.

Discontinuation due to Adverse Events

AE leading to discontinuation are shown in Table 20 on pooled data. The most frequent events leading to discontinuation were dyspepsia and abdominal pain. The frequency of GI AE leading to discontinuation was higher in the placebo group compared with the esomeprazole groups. The frequencies of other AE leading to withdrawal were similar across groups.

Table 20.

Adverse events leading to discontinuation by System Organ Class, N (%) of patients[a], safety population (pooled data from Study D9617C00011 and Study D961FC00003)

System organ class	E20 n=1286	Placebo n=1295
Gastrointestinal disorders	20(1.6%)	38(2.9%)
Nervous system disorders	11(0.9%)	13(1.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7(0.5%)	10(0.8%)
Cardiac disorders	6(0.5%)	3(0.2%)
Respiratory, thoracic and mediastinal disorders	6(0.5%)	0(0%)
General disorders and administration site conditions	2(0.2%)	5(0.4%)
Infections and infestations	4(0.3%)	4(0.3%)
Skin and subcutaneous tissue disorders	4(0.3%)	4(0.3%)
Blood and lymphatic system disorders	3(0.2%)	0(0%)
Injury, poisoning and procedural complications	0(0%)	2(0.2%)
Investigations	1(0.1%)	3(0.2%)
Musculoskeletal and connective tissue disorders	2(0.2%)	2(0.2%)
Reproductive system and breast disorders	0(0%)	2(0.2%)
Ear and labyrinth disorders	1(0.1%)	0(0%)
Eye disorders	1(0.1%)	0(0%)
Hepatobiliary disorders	1(0.1%)	0(0%)
Metabolism and nutrition disorders	1(0.1%)	1(0.1%)
Psychiatric disorders	0(0%)	1(0.1%)
Vascular disorders	1(0.1%)	0(0%)

E20 esomeprazole 20 mg od.

[a] Patients reporting at least 1 DAE after first dose of investigational product.

Postmarketing experience

Axanum had not been marketed in any country at the time of the clinical evaluation report.

Evaluator's overall conclusions on clinical safety

In general, the combination of esomeprazole 20 mg or 40 mg and low-dose ASA was well tolerated during 26 weeks treatment. The pattern and frequencies of AE recorded in the two Phase III studies were similar in the esomeprazole and placebo groups. There were no clinically significant differences in laboratory measurements, vital signs or ECG between the treatment groups. The incidence of SAE was low and similar in both treatment groups although cerebrovascular SAE occurred slightly more frequently in the esomeprazole groups. Older patients who were ≥65 years of age had slightly more AE than younger patients but gender did not influence safety outcomes in either study. Blacks appeared to have fewer AE than other races but the numbers of Blacks treated was relatively small.

There were eleven deaths in the overall safety population. In Study D9617C00011, two deaths (ischaemic stroke and bladder cancer) occurred in the placebo group with none in the E20 group. A further nine deaths occurred in Study D961FC00003. Five of these deaths were attributed to cardiac causes and, of these, four occurred in patients treated with esomeprazole and one in a patient who received placebo. The patient population was at high risk of cardiac events and the number of deaths was small. Nonetheless, the apparent excess of cardiac deaths in the esomeprazole groups might possibly reflect a reduced protective effect of the co-administered low-dose ASA. However, Study D961FC00011 showed no effect of esomeprazole on platelet function when ASA 81 mg was administered, making a causal relationship less likely.

The frequency of peptic ulcers was low in all treatment groups. There was a small ARR in favour of esomeprazole in both Phase III studies although the benefit for duodenal ulcer was marginal. AstraZeneca propose that peptic ulcer is a surrogate for complications of peptic ulcer but the frequency of upper GI complications (bleeding, perforation and obstruction) was very low in both studies. Complications assumed to originate in the upper GI tract reported in both studies were marginally more common in the placebo groups compared with the esomeprazole groups. However, the opposite trend was observed for lower GI tract bleeding. Seven cases of haematochezia occurred in the esomeprazole groups compared with none in the placebo groups.

Clinical summary and conclusions

Pharmacokinetics

The free combination of 40 mg esomeprazole capsules and 325 mg aspirin tablets was bioequivalent to the fixed-dose combination capsule of esomeprazole 40 mg and low-dose acetylsalicylic acid 325 mg.

There was no PK interaction between 40 mg esomeprazole capsules and 325 mg low-dose acetylsalicylic acid tablets following 5 days of repeated oral administration in healthy subjects.

A waiver was sought by the sponsor regarding the *in vivo* bioequivalence of the 81/20 mg combination tablet with the free forms tablets. The request was based upon demonstration of bioequivalence for the highest strength combination tablet under development (325/40 mg), dose-proportionality of the other strengths to the strength on which bioequivalence testing was undertaken, and comparative *in vitro* dissolution profiles with regard to ASA and esomeprazole for all strengths of the ASA/esomeprazole products. This has been discussed previously in this report, with the conclusion that a waiver was justified.

Pharmacodynamics

Low-dose ASA (75 to 325 mg daily) is a platelet inhibitor that selectively inhibits COX-1. Esomeprazole is a proton pump inhibitor, which suppresses gastric acid secretion by irreversible binding and blocking of the gastric H+/K+-ATPase, the proton-transporting enzyme involved in the production of hydrochloric acid in the stomach. Registration of a combination tablet is being sort for prevention of cardio- and cerebrovascular events in patients requiring continuous low-dose ASA treatment and at risk of developing ASA associated gastric and/or duodenal ulcers.

Esomeprazole (20 mg) did not affect the anti-platelet activity of aspirin (81 mg).

Clinical efficacy

Clinical efficacy was assessed in two Phase III studies including 2426 patients receiving low-dose ASA (75 to 325 mg daily) for the secondary prevention of cardiovascular events and who were at risk of developing peptic ulcers. Esomeprazole, 20 mg and 40 mg od, reduced the occurrence of peptic ulcers in both studies with RRR >70%. However, ARR was much lower in both studies with benefits in favour of the esomeprazole arms ranging from 3.8% to 5.6%. Gastric ulcer occurred less frequently in the esomeprazole arms compared with placebo in both studies. Duodenal ulcer occurred less frequently in patients receiving esomeprazole in both arms of Study D961FC00003 but, based on confidence intervals, there was no apparent benefit in favour of esomeprazole in Study D9617C00011. The sponsor claim that peptic ulcers are a surrogate marker of peptic ulcer complications, and there is an extensive literature to support this. However, there was little evidence to support this proposal in the studies presented. Peptic ulcer rates were low and complications of ulcer, including bleeding, perforation and obstruction, occurred infrequently in both studies. Event numbers were too small to permit meaningful comparison. However, there was little to support the hypothesis that esomeprazole treatment prevents peptic ulcer complications in this patient population.

Esomeprazole 20 mg and 40 mg significantly reduced dyspeptic symptoms and GORD compared with placebo. However, as noted with peptic ulcer, the absolute differences in symptom frequencies between the esomeprazole groups and placebo were not marked. In Study D961FC00003 in patients with no dyspepsia at baseline, 81.3% of patients receiving placebo remained symptom free compared with approximately 89% in the esomeprazole groups. The corresponding figures for GORD were 78.3% and approximately 86%, respectively. It should also be noted that rescue antacid medication for dyspepsia and GORD was required infrequently in patients receiving esomeprazole or placebo (a mean of 0.3 tablets per day in patients receiving placebo compared with 0.2 tablets per day in patients receiving esomeprazole). Esomeprazole 20 mg and 40 mg also reduced the frequency of gastric and duodenal erosions compared with placebo. The benefits were maintained in sub-groups defined by age, sex, and GI risk factors. The benefit was also maintained in patients receiving all ASA doses in the range 75 to 325 mg daily. However, it should be noted that there was a positive relationship between peptic ulcer and ASA dose: in Study D961FC00003, peptic ulcer in the placebo group occurred in 6.1% of patients using ASA in doses of 75 to 100 mg daily, compared with 8.7% of patients using ASA 101 to 325 mg daily. Patients who received lower ASA doses had a lower frequency of peptic ulceration. In markets such as Australia, where >70% of ASA use is in the 81 to 100 mg range, ARR for peptic ulcer frequency in favour of esomeprazole may be even less clinically meaningful than in the overall population.

Approximately 22% of randomised patients were subsequently shown to be H. pylori positive based on UBT performed at the first study visit but clinical outcomes were similar in H. pylori positive and negative groups. H. pylori infection increases the risk of peptic

ulcer so there is no evidence on which to exclude these patients from esomeprazole prophylaxis.

Clinical safety

Clinical safety was assessed in 3395 patients in the Phase III studies: 814 patients received E40, 1286 patients received E20 and 1295 patients received placebo. The planned duration of treatment was 26 weeks. The actual exposure was 166 days the 1281 patients who received E20 compared with 156 days in the 1292 patients who received placebo. The most commonly reported AE were infections and gastrointestinal events (upper respiratory infections and diarrhoea respectively). Most AE were mild, similar across treatment groups and comparable with the known safety profiles of esomeprazole and ASA. The number of deaths in the pooled data was low; four patients in the E20 group and three in the placebo group. However, nine patients (four receiving E40, four receiving E20 and one receiving placebo) died in Study D961FC00003, a study which included patients with more cardiovascular risk factors than Study D9617C00011. Five of the nine deaths were cardiac in origin (two patients in the E40 group, two patients in the E20 group and one in patients receiving placebo) and they all had significant cardiovascular risk factors. None of the deaths were thought to be causally related to drug treatment but there is an obvious concern that ASA effectiveness may have been reduced in patients receiving esomeprazole. The frequencies of SAE other than death were similar across treatment groups. However, SAE relating to cerebrovascular disorders occurred in 10 (0.5%) patients during esomeprazole treatment compared with 2 (0.2%) during treatment with placebo. These events also raise concern of reduced ASA effectiveness in patients who received ASA in these studies (or who will receive Axanum if approved).

There were no clinically significant changes in clinical chemistry or urinalysis variables in any treatment group over time. Similarly, there were no clinically significant changes or differences between treatments in vital signs or ECG.

Benefit risk assessment

Benefits

The data presented in the two Phase III studies confirms that, compared with placebo, esomeprazole reduces the frequency of peptic ulcer, duodenal and gastric erosions, symptoms of dyspepsia and GORD over a 26 week treatment period in patients receiving low-dose ASA. The frequency of peptic ulcers in the placebo group was significantly lower than that reported in the literature but the pattern of morbidity and the response to treatment with a PPI were similar. The benefits of esomeprazole, in doses of 20 mg and 40 mg od, were comparable in sub-groups defined by age, gender, race and H. Pylori status. RRR was over 70% in favour of both doses of esomeprazole ($p<0.0001$) compared with placebo although absolute risk reductions were modest. Complications of peptic ulcer were few in all treatment groups, although there was a marginal benefit in favour of esomeprazole compared with placebo.

Compliance for the fixed dose combination (FDC) compared with the individual components (esomeprazole and ASA) was not tested but there is strong literature support for increased compliance with FDC. It is possible that increased compliance with ASA in the FDC might lead to a significant reduction in cardiovascular events in patients receiving ASA for primary or secondary prevention.

Risks

Esomeprazole was well tolerated and the frequency of AE was similar compared with placebo. SAE were also similar in frequency in the esomeprazole and placebo treatment

groups although there was a slight excess of cerebrovascular SAE in the esomeprazole groups. There was a numerical excess of fatal SAE in both esomeprazole groups compared with placebo with five related to likely cardiac causes. There is a possibility that ASA effectiveness is reduced when co-administered with esomeprazole. However, drug-drug interaction studies showed no effect of esomeprazole on ASA PK (esomeprazole 40 mg and ASA 325 mg), or on ASA PD (platelet aggregation and serum TXB2). The deaths occurred in patients at high risk of cardiovascular events so it is possible that the excess of deaths in the esomeprazole groups was co-incidental.

Safety specification

In the clinical development program, 104 healthy subjects and 2100 patients received ASA (in the dose range 75-325 mg daily) plus esomeprazole. Of the 2100 patients who received esomeprazole, 1308 were exposed for at least 6 months and the longest exposure was 7.4 months. The FDC (Axanum) was given only to the healthy participants in the bioequivalence Study D961FC00002. All other healthy subjects and patients received esomeprazole and a variety of commercially available low-dose ASA formulations. Of the 2095 patients treated with low-dose ASA plus esomeprazole in the Phase III studies, 152 patients were treated with the targeted dose ASA 81 mg with esomeprazole 20 mg. Of the 2095 patients in the Phase III studies, 1479 (70.6%) were aged ≥65 years. Of those who received the indicated dose, 114 (75.0%) were aged ≥65 years and no specific safety concerns were apparent in this age group. A total of 1744 White patients were exposed for a person time of 798.2 years with 74 Black patients, 176 Orientals and 101 patients of other races exposed for a total of 954.5 person years.

The postmarketing exposure for low-dose ASA was unknown at the time of this AusPAR although it has been widely prescribed for decades under a variety of trade names. Since it was first marketed in 2000, more than 1030 million patient treatment courses of oral esomeprazole have been delivered to wholesalers in 115 countries. Patients not studied include children, pregnant women and lactating mothers.

The sponsor seeks approval of Axanum for patients who require aspirin for the prevention of cardiovascular disease in combination with esomeprazole for the prevention of ulcers associated with aspirin use. Patients most likely to benefit from a fixed dose combination are those with risk factors for ulcers including age ≥60 years in those with a history of coronary artery disease, or age ≥65 years.

Most safety issues associated with esomeprazole have been well characterised or are under continuing evaluation. A continuous safety review and evaluation for Axanum is proposed within existing AstraZeneca (AZ) pharmacovigilance processes. This includes a global safety database which records SAE from all clinical trials, AE associated with the use of all marketed AZ products, and pregnancy and overdose data. The safety specifications outlined in the RMP are consistent with the clinical trial data presented in the submission.

Balance

The two Phase III studies together demonstrated a reduced frequency of peptic ulcers in patients receiving low-dose ASA when treated with esomeprazole 20 mg or 40 mg od. The RRR in favour of esomeprazole was approximately 70% but the ARR was modest. There are similar modest reductions in symptoms of dyspepsia and GORD, and upper GI tract erosions in patients treated with esomeprazole compared with placebo. There was a reduction in the frequency of gastric ulcer with esomeprazole treatment but a reduction in the frequency of duodenal ulcer was shown in only one of the two pivotal studies. Peptic ulcer is used as a surrogate marker of peptic ulcer complications, including bleeding, perforation and obstruction. However, although the studies were not powered to show a difference in peptic ulcer complications, there appeared to be only a minor trend in favour of esomeprazole compared with placebo in the two studies. Decreased frequencies of peptic ulcers, symptoms and endoscopic abnormalities were observed in patients

receiving all doses of ASA in the range 75 to 325 mg. However, patients receiving lower doses of ASA, in the range 75 to 100 mg, had fewer endpoints than patients receiving 101 to 325 mg. Therefore, it is possible that the modest benefits in favour of esomeprazole would be even less favourable in Australia where ASA 100 mg od is prescribed to the majority of users.

From the data submitted, it was considered that there was a substantial argument in favour of on-demand treatment with esomeprazole. However, increased overall compliance with ASA may be expected to reduce the frequency cardiovascular events, including death, in low-dose ASA users.

The benefits in favour of esomeprazole are off-set by a potential risk of reduced ASA effectiveness. However, the drug-drug interaction studies are reassuring. There is also a risk of adverse drug reactions associated with long-term esomeprazole use. The adverse event profile of esomeprazole is well understood although well publicised potential risks such as hip fracture are difficult to quantify.

The use of PPI for the prevention of peptic ulcer in patients receiving low-dose aspirin is widely accepted. For example, the American College of Gastroenterology and American Heart Association jointly recommend the use of PPI in patients at risk of developing peptic ulcer. They also recommend that the dose of low-dose ASA should not exceed 81 mg daily. In general, the findings of the two Phase III studies support these recommendations. The possibility that esomeprazole reduces ASA effectiveness is raised by the excess of deaths in the esomeprazole treatment groups compared with placebo. However, the overall numbers were small and the excess deaths could have arisen by chance. Increased compliance with ASA therapy may lead to improved outcomes[14] in patients with cardiovascular risk factors although this cannot be confirmed without a large prospective study. The overall benefit risk balance was considered favourable.

Conclusions

The efficacy benefit in favour of esomeprazole was of only marginal clinical significance but it is sufficient to support approval. Risk reduction for DU was demonstrated in only one study; however, the indication sought is not for DU but for peptic ulcer. There was no difference in risk reduction between the E20 and E40 doses; however, this conclusion supports the submission for the esomeprazole 20 mg dosage only.

The proposed indication is prevention of ulcers associated with aspirin use and, as discussed above, the justification for the use of low dose ASA should be based on usage guidelines and is the responsibility of the prescriber Prophylaxis in patients receiving and low dose ASA is widely recommended12, based on a number of published prevention trials. There was a trend towards a reduced risk of peptic ulcer complications with esomeprazole in the submitted studies. However, event numbers were low and the studies were not powered to detect a statistically significant difference. This information might be desirable and medically important; however, the sponsors make no such efficacy claim.

The efficacy studies were not powered to detect significant differences between the lowest and highest doses of ASA. However, there were no meaningful differences other than an increased likelihood of GI events in patients receiving higher ASA doses. This issue is of minor relevance in the Australian context where the great majority of usage is in the 75-100 mg range.

The overall benefit risk balance of Axanum was considered positive (although marginal) based on the study data presented. Registration approval was recommended.

[14] Fixed dose combinations improve medication compliance: a meta-analysis. Bangalore S et al, Am J Med (2007) 120: 713-719.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The summary of the Ongoing Safety Concerns as specified by the sponsor is summarised in Table 21 below.

Table 21. Summary of Ongoing Safety Concerns

Important Identified Risks	Agranulocytosis Allergic reactions/Hypersensitivity reactions Depression Asthma, Bronchospasm Severe gastrointestinal bleeding Hepatitis, Hepatic failure, Hepatic encephalopathy Erythema Multiforme, Stevens Johnson syndrome/Toxic Epidermal Necrolysis Hypomagnesaemia Interstitial nephritis
Important Potential Risks	Blindness/Blindness transient Rhabdomyolysis Osteoporosis/Osteoporotic fractures Haemolytic Anaemia Convulsion/Seizure Cutaneous Lupus Erythematosus Potential interaction with clopidogrel/Potential interaction with valproate
Newly identified safety concerns	Interaction between methotrexate and esomeprazole Convulsion/Seizure Cutaneous Lupus Erythematosus Interaction between valproate and esomeprazole Interaction between aspirin and esomeprazole
Important missing information	Pregnant and lactating women Fertility Patients with renal impairment
Identified and potential interactions	Anticonvulsants Anticoagulant therapy/Inhibitors of platelet aggregation other than aspirin including warfarin and other coumarin derivatives NSAIDs Methotrexate Oral hypoglycaemics Phenytoin Atazanavir Nelfinavir Digoxin Clopidogrel Valproate

OPR reviewer comment

Cardiovascular events have not been considered as a potential risk to be included in the safety specification in the RMP. The sponsor concluded that there was insufficient evidence at this time. It was noted that the sponsor was conducting studies to further define the potential interaction with clopidogrel and PPIs, and aspirin and PPIs.

Pharmacovigilance plan

Proposed pharmacovigilance activities

Routine pharmacovigilance has been proposed by the sponsor for the safety concerns including *Potential interaction with clopidogrel*, *Potential interaction with low-dose-ASA* and *Other important identified and potential risks and important missing information*.

The sponsor also proposed additional pharmacovigilance in the form of additional clinical studies. Table 22 provides a summary of the proposed pharmacovigilance activities.

Table 22. Proposed pharmacovigilance activities

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Potential interaction with clopidogrel	In addition to routine pharmacovigilance activities, a pharmacoepidemiological study (D9612HN00014) of the potential interaction between clopidogrel and PPIs is ongoing. In addition, 2 PK/PD studies (D961C00010 & D9612C00034) are initiated.	Routine risk minimisation activities, as described in the RMP, are considered to be sufficient.
Potential interaction with low-dose-ASA	Two pharmacoepidemiological studies (D961FN00006 & D961FN00007) are planned to further evaluate the potential interaction between low dose aspirin and PPIs	Routine risk minimisation activities, as described in the RMP, are considered to be sufficient.
Other important identified and potential risks and important missing information, as described in RMP	Routine pharmacovigilance process.	Routine risk minimisation activities, as described in the RMP, are considered to be sufficient.

OPR reviewer's comments

See also *Summary of Recommendations* below.

Advisory Committee on the Safety of Medicines (ACSOM) provided the following advice regarding studies D961FN00006 and D961FN00007:

> *"The committee agreed that the two pharmacoepidemiological studies ……were neither sufficient nor adequate to address the issue of a potential association between concomitant use of low dose aspirin and PPIs with the risk of acute myocardial infarction or death due to coronary heart disease.*
>
> *The committee advised that concomitant use of PPIs and aspirin may reduce the bioavailability of the latter, resulting in reduced inhibition of platelet aggregation. They noted that recent studies17,54 raise concerns that treatment with PPIs significantly reduces aspirin-induced inhibition of platelet aggregation but their results are not definitive. Furthermore, the two proposed observational pharmacoepidemiological studies are in patients with a previous ischemic*

cerebrovascular or cardiovascular event; thus the studies will not address the concern.

The Committee believed that in order to fully address the question, prospective, preferably randomised, studies were required. The Committee believed such studies were warranted given the widespread use of low dose aspirin'."

A concern was that the aspirin-PPI co-administration to be studied in D961FN00006 was for the secondary rather than the primary prevention of cardiovascular disease, as is a frequent prescribing pattern in Australia.

Risk minimisation activities

The sponsor describes the identified and potential risks for Axanum as being linked to the two components (low-dose aspirin and esomeprazole).

The sponsor states that routine risk minimisation activities are considered to be sufficient, and therefore no additional risk minimisation activities were considered necessary.

OPR reviewer comment:

The sponsor's identified risk minimisation plan would seem focussed on the risk minimisation activities for clinical trials. No detailed account of how the sponsor believes the safety concerns are addressed by the product labelling was included in the RMP. Of specific interest there will be no routine risk minimisation activity for the Important Potential risks. There was no specific referencing of the proposed Australian PI in the RMP and it was proposed that this should be addressed in the Australian specific annex of the RMP such that the sponsor clearly identifies how each safety concern is addressed in the labelling. (Note; the sponsor states these are addressed in the labelling section of the RMP).

If the results of the studies listed in the pharmacovigilance plan indicate a change should be made to the safety specifications an updated RMP will be required. Details of any new additional pharmacovigilance and risk minimisation activities around new safety specifications should be submitted with the updated RMP.

Amendments to the draft PI were recommended. In regard to the proposed routine risk minimisation activities, the draft consumer medicine information should align with the PI.

Potential for medication errors

The sponsor's argument that a single strength and single dosage regimen will lower the risk of medication errors was accepted.

The sponsor did not indicate that there may be safety concern with crushing or chewing the tablet but has not provided a rationale for this advice.

Summary of recommendations

The OPR provided these recommendations in the context that the submitted RMP was supportive to the application; the implementation of a RMP Version 2 dated 9 June 2011 including the sponsor's responses questions was imposed as a condition of registration with the following qualification:

It was recommended the sponsor expand the Australian specific annex. The Australian specific annex of the EU RMP should include the following:

A description of the pharmacovigilance plan if it differs that outlined in the EU RMP, and if not, this should be made clear.

A section identifying how the Australian PI addresses each safety concern in terms of risk minimisation. This could be in a tabulated form.

Pharmacovigilance Plan

The description of the routine pharmacovigilance activity in Section 3 of the RMP aligns *with 3.2.1 Routine pharmacovigilance practices. Note for guidance on planning pharmacovigilance activities (CHMP/ICH/5716/03)*. The sponsor indicated in Annex 9 that a description of the AstraZeneca Pharmacovigilance System was available on request. There was a lack of clarity regarding the pharmacovigilance activities the sponsor will actually undertake in Australia as a result of this statement, which should be rectified by the sponsor.

If the abovementioned studies indicate a change should be made to the safety specifications an updated RMP will be required. Details of any new additional pharmacovigilance and risk minimisation activities around new safety specifications should be submitted with the updated RMP.

With respect to the potential interaction with clopidogrel, the sponsor has indicated that the outcome of Study D9612N00012, called D9612N00014 in the RMP, at interim analysis has not shown an association between clopidogrel and PPI use. The sponsor was requested to provide a summary of the results of this study at its conclusion. The sponsor indicated that the results from Study D961FC00010 were expected at the end of 2011. The sponsor was requested to provide a summary of the study outcome when the conclusions were known.

ACSOM provided the advice that Studies D961FN00006 and D961FN00007 were unlikely to answer the question of a potential association between concomitant use of low dose aspirin and PPIs and the concomitant use of clopidogrel and PPIs with the risk of myocardial infarction or death due to coronary heart disease. It was suggested consideration be given to a prospective randomised study to address this issue, as recommended by ACSOM.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The quality evaluator has recommended approval of the submission with respect to chemistry and quality control. With respect to bioavailability, the quality evaluator has commented that:

- Study D961FC00002 showed bioequivalence of a 325/40 fixed-dose capsule to the monotherapies used in the Phase II clinical studies and it was accepted that this could be extrapolated to the proposed 81/20 mg capsule.
- It was accepted that the US aspirin product used in the Phase III clinical studies and the bioavailability study could be used as a surrogate comparator rather than an Australian aspirin product.
- It was accepted that patients may switch from Australian 20 mg Nexium tablets to the proposed fixed dose combination product without a change in the bioavailability of esomeprazole.

- It was also accepted that no bioavailability studies were required to investigate the absolute bioavailability and effect of food in relation to the fixed-dose combination capsules.
- The application was presented to the 140th meeting of the Pharmaceutical Subcommittee (PSC) of the ACPM in August 2011. The PSC recommended some changes to the PI which the Delegate endorsed.

Nonclinical

The nonclinical evaluator made the following comments:

- No data were submitted on potential pharmacodynamic interactions of the combination and the potential for such interactions will therefore rely on the clinical data.
- In the 3 month repeat dose studies in dogs, systemic exposure to esomeprazole when administered in combination with aspirin was approximately 25% lower than when administered alone.
- No firm conclusions could be drawn from the nonclinical data on the possible effect of esomeprazole co-administration on systemic exposure to aspirin in dogs.
- The ratio of systemic exposures to esomeprazole and salicylic acid in the 3 month toxicity study in dogs were comparable to the predicted ratio in humans with the proposed combination.
- There was no evidence of any new or unexpected toxicological effect when esomeprazole and aspirin were co-administered and the incidence and severity of toxic effects were consistent with additivity.
- Both active substances have been approved and on the market for many years and there are extensive nonclinical and clinical data available for the individual components. Furthermore, esomeprazole is currently approved to be used in free combination with aspirin for the proposed indication. In conclusion, there were no nonclinical objections to the registration of Axanum.
- The Delegate endorsed the nonclinical evaluator's recommended changes to the PI.

Clinical

There following six TGA adopted European guidelines were considered relevant to this submission, besides the general guidelines:

CPMP/EWP/240/95 Rev. 1
Guideline on Clinical Development of Fixed Combination Medicinal Products
Replaces: pp. 175 - 180 of Rules 1998 (3C) - 3CC10a
Published: TGA Internet site Effective: 28 May 2010

pp. 127 - 132 of Rules 1998 (3C) - 3CC6a
Clinical Investigation of Medicinal Products for Long-Term Use
Replaces: pp. 163 - 165 of Rules 1989
Effective: 12 February 2002
See also: pp. 121 - 125 of Rules 1998 (3C) - 3CC5a (Adopted by TGA with conditions)

EMEA/CHMP/EWP/311890/2007
Guideline on the Evaluation of Medicinal Products for Cardiovascular Disease Prevention
Published: TGA Internet site
Effective: 29 June 2009

EMEA/CHMP/EWP/297931/2008
Concept Paper/Recommendation on the Need for Revision of (CHMP) Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95)
Published TGA Internet site for information only, effective: 10 February 2009

CPMP/EWP/560/95
Note for Guidance on the Investigation of Drug Interactions
Published: TGA Internet site
Effective: 19 April 2001

CPMP/EWP/QWP/1401/98
Note for Guidance on the Investigation of Bioavailability and Bioequivalence
Replaces: pp. 231 - 244 of Rules 1998 (3C) (Adopted by TGA 12 February 2002)
Published: TGA Internet site Effective: 10 April 2002[15]

The clinical evaluator has provided a report on the submitted data, which included the following:

- Two randomised, Phase III, double-blind, 26 week, efficacy and safety studies, the first study (D9617C00011) comparing esomeprazole 20 mg + low-dose aspirin versus placebo + low-dose aspirin and the second study (D961FC00003) comparing esomeprazole 20 or 40 mg + low-dose aspirin versus placebo + low-dose aspirin.
- Study D961FC00011 examined platelet aggregation and serum TXB2 in a pharmacodynamic interaction study.
- Study D961FC00001 was a pharmacokinetic drug-drug interaction study which investigated the potential interaction between esomeprazole and aspirin. It was conducted using the highest proposed doses of each study medication, namely, esomeprazole 40 mg once daily and aspirin 325 mg once daily.
- The Phase III studies were performed using a free combination of a clinical trial esomeprazole capsule or matching placebo and commercially available aspirin tablets. Evidence of bioequivalence between the fixed-dose and free combinations of esomeprazole and aspirin was investigated in Study D961FC00002. This trial was also performed using the highest proposed doses of each study medication, namely, esomeprazole 40 mg once daily and aspirin 325 mg once daily.

The clinical evaluator recommended approval in the evaluation report. The evaluator was of the opinion that the efficacy benefit in favour of esomeprazole was only of marginal clinical significance but was sufficient to support approval. Risk reduction for duodenal ulcer was demonstrated in only one of the pivotal studies. However, as further noted by the evaluator, the indication sought involves peptic ulcer and not duodenal ulcer. There was no difference in risk reduction between the esomeprazole 20 mg and the esomeprazole 40 mg doses.

[15] Adopted by TGA with the following notation:
"While this guidance suggests that the design and conduct of the study should follow EU regulations on Good Clinical Practice, sponsors should note that the EU Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) has been adopted in Australia with TGA annotations.
The procedure for abridged applications claiming essential similarity to a reference product (ie, generics), which allows applications to be made to numerous Member States of the EU, based on bioequivalence with a reference product from one Member State, does not apply in Australia. An application for registration of a generic product in Australia should generally include a bioequivalence study versus a leading brand obtained in Australia."

Pharmacokinetics

Study D961FC00002 was a Phase I, open-label, randomised, single-centre, 2-stage group sequential design, 2-way crossover bioequivalence study which compared the pharmacokinetics of a fixed-dose combination capsule of esomeprazole 40 mg and low-dose aspirin 325 mg with a free combination of esomeprazole 40 mg capsule and low-dose aspirin 325 mg tablet following a single oral dose in 49 healthy subjects (29 female), aged 20 to 50 years. The median T_{max}, mean $t_{1/2}$, AUC and C_{max} of esomeprazole, acetylsalicylic acid (aspirin) and salicylic acid were similar for the fixed and free combinations and all bioequivalence criteria were satisfied.

It should be noted that the present application is for a fixed-dose combination capsule containing 20 mg esomeprazole enteric-coated pellets and 81 mg immediate release aspirin for oral administration. The sponsor submitted a comprehensive justification for the waiver of the requirement for a bioequivalence study examining the fixed and free combinations of 20 mg esomeprazole and 81 mg aspirin, on the basis that, amongst other things, the results of the Study D961FC00002 (involving the higher doses, esomeprazole 40 mg and aspirin 325 mg), could be extrapolated to the lower-dose scenario. The Delegate concurred with the clinical evaluator as to the acceptability of the sponsor's justification for a bio-waiver.

Study D961FC00001 was a single-centre, open-label, randomised, 3-way crossover drug-drug interaction study which examined the PK interaction between 40 mg esomeprazole capsules and 325 mg aspirin tablets following 5 days of repeated oral administration in 55 healthy subjects (38 female) aged 20 to 49 years. Each treatment period was separated by a wash-out period of at least 13 days. The 90% confidence intervals for the ratios of the geometric means of AUCt and Cmaxss for each of esomeprazole and aspirin (in combination versus alone) were all within the required [80%, 125%] limits, indicating the lack of a PK interaction between the two drugs.

Pharmacodynamics

Study D961FC00011 was a Phase I, open-label, 2-way crossover, drug-drug interaction study which evaluated the effect of esomeprazole 20 mg once daily on the pharmacodynamics of aspirin 81 mg once daily after 5 days of treatment in 29 healthy subjects (8 female) aged 19 to 75 years (Treatment A: aspirin alone for 5 days and Treatment B: aspirin + esomeprazole as free combination). There was little difference in platelet aggregation, as measured by aspirin reactivity units (ARU) when aspirin was given alone (delta ARU from Day 1 to Day 6 = 0.7001) or in combination with esomeprazole (delta ARU = 0.7146). Similarly, there was little difference in the effect of aspirin on TXB2 concentrations, either when given alone or in combination with esomeprazole (Day 6/Day 1 ratios of 0.0041 and 0.0045, respectively).

Efficacy

As noted earlier, there were 2 pivotal Phase III studies, D9617C00011 and D961FC00003, conducted to demonstrate that esomeprazole 20 mg and 40 mg once daily reduces the rate of gastric and duodenal ulcers in patients taking low-dose aspirin who are at risk of developing peptic ulcers. Both were randomised, double-blind, 26-week studies performed in patients receiving esomeprazole 20 mg, esomeprazole 40 mg or matching placebo on a background of continuous low-dose aspirin prophylactic treatment.

First pivotal Study D9617C00011 (ASTERIX)

This was a Phase III, randomised, multi-centre, double-blind, placebo-controlled study to assess the degree of prevention of low-dose aspirin associated gastroduodenal lesions and upper gastrointestinal symptoms in patients taking esomeprazole 20 mg once daily for 26 weeks.

Key inclusion criteria were that subjects be males or females with the medical need (cardiovascular or cerebrovascular) for daily low-dose aspirin for the duration of the study, age > 60 years, no gastric or duodenal ulceration at baseline endoscopy and no evidence of *H. pylori* infection by conventional testing.

The primary efficacy endpoint was the incidence of gastric and/or duodenal ulceration at endoscopy in a 26-week period in patients taking low-dose aspirin. Endoscopy of the oesophagus, stomach and duodenum was performed at baseline, 8 weeks and 26 weeks, or at premature discontinuation or when clinically indicated. Secondary endpoints were the incidence of oesophageal lesions according to the Los Angeles (LA) classification, upper GI symptoms as assessed by the investigator at each visit and adverse events, laboratory parameters and vital signs.

The safety population included all patients who had taken at least one dose of study medication. The ITT population consisted of all randomised patients without gastric or duodenal ulceration at baseline and the PP population consisted of all patients who met the inclusion and exclusion criteria. Primary and secondary endpoints were evaluated using the ITT population and the primary endpoint was also evaluated in the PP population. The log-rank test was used to analyse differences between the esomeprazole and placebo treatment groups. A sample size of 960 patients (480 per group) was required to provide 90% power to detect a 6.5% difference in ulcer occurrence rates [6.5% for the esomeprazole group and 13% for the placebo group].

Randomisation was 1:1 to either the esomeprazole 20 mg treatment arm or the matching placebo arm.

Results of pivotal Study D9617C00011

A total of 1153 patients were enrolled and 992 patients were randomised and 815 patients completed the study. H. pylori infection and ulcers detected at baseline were the main reasons for patients failing to be randomised. There were 991 patients in the ITT group, 981 in the safety group and 612 patients in the PP group.

The baseline characteristics were similar in both treatment groups and in both analysis sets. The mean age in both groups was approximately 69 years and in the ITT population, 40.4% of the esomeprazole group and 37.1% of the placebo group were aged > 70 years (41.4% and 34.1%, respectively, in the PP population). About 57% were male and the great majority were Caucasian (approximately 89%). Approximately 22.5% of patients in each group were H. pylori positive and were excluded from the PP analysis set.

In the ITT population, there was a lower cumulative incidence of gastric and/or duodenal ulcers in the esomeprazole 20 mg group compared with the placebo group over the 26-week treatment period. Similar results were observed for the PP analysis set.

During the 26-week treatment period, gastric ulcer and/or duodenal ulcer occurred in 6.2% of placebo patients and 1.8% of the patients taking esomeprazole 20 mg, with a relative risk reduction of 70%. The PP analysis did not include patients who were H. pylori positive and, as noted by the clinical evaluator, the comparable efficacy results suggest that esomeprazole 20 mg has a similar effect in both H. pylori positive and negative patients.

The secondary efficacy results were generally supportive of the primary efficacy results. The cumulative occurrence of oesophageal lesions was significantly lower at 26 weeks in

the esomeprazole 20 mg group (1.7%) compared with that in the placebo group (11.5%), p < 0.0001. The occurrences of epigastric pain, epigastric burning, heartburn and acid regurgitation were all significantly lower in the esomeprazole 20 mg group compared with those in the placebo group at month 2. Similar responses were observed at Months 4 and 6 with varying levels of statistical significance. The mean number of antacid rescue tablets taken per day was low and similar in both treatment groups.

In the primary evaluation of efficacy in this pivotal study, the evaluator made no mention of the evaluation of the rates of gastric ulcer and duodenal ulcer, considered separately. There is a brief mention at the end of the Efficacy section that for gastric ulcer, the ARR in favour of esomeprazole 20 mg was 2.6% in this study and that for duodenal ulcer, the ARR in favour of esomeprazole 20 mg was 1.2% (95% CI [0.0%, 2.4%]).

Second pivotal Study D961FC00003 (OBERON)

This was a Phase III, randomised, double-blind, parallel-group, multicentre to assess the effect of esomeprazole 20 or 40 mg once daily versus placebo on the occurrence of peptic ulcers during 26 weeks in subjects on continuous low-dose aspirin.

Key inclusion criteria included physician initiated low-dose aspirin (75-325 mg daily) expected to continue for the duration of the study, H. pylori negative at screening. In addition, subjects were required to fulfil at least one of the following criteria:

- At least 65 years of age
- Aged at least 18 years and with a documented history of uncomplicated ulcer
- At least 60 years of age and naive to low-dose aspirin
- At least 60 years of age with stable coronary artery disease
- Aged at least 60 years with upper GI symptoms requiring an endoscopy and with the finding of at least five gastric or duodenal erosions.

The primary efficacy endpoint derived from endoscopy was the time to occurrence of peptic ulcer. Secondary endpoints were time to occurrence of gastric ulcer, time to occurrence of duodenal ulcer, the number of gastric and/or duodenal erosions, patient reported dyspeptic and GORD symptoms as assessed by the Reflux Disease Questionnaire (RDQ) and upper GI symptom assessment by the investigator.

All patients who received at least one dose of study drug were included in the safety analysis. The ITT set included all patients without a peptic ulcer who were randomised at baseline and the PP set included all patients randomised without major protocol inclusion/exclusion criteria violations. Primary and secondary endpoints were analysed in the ITT set and the primary endpoint was analysed in the PP set. The log-rank test was used to assess the differences between the esomeprazole groups and the placebo groups. The sample size of 2400 (800 in each arm) was based on the first pivotal study, D9617C00011 (ASTERIX). A higher placebo event rate of 8% was assumed because the study population was in a higher risk category. The relative risk reduction for peptic ulcer was assumed to be 60% which implied an event rate of 3.2% in the esomeprazole group. The study had 90% power to detect a significant difference in the primary endpoint with a significance level of 0.025 and a drop out rate of 15%.

Subjects were centrally randomised 1:1:1 to receive capsules containing esomeprazole 20 mg or esomeprazole 40 mg or placebo.

Results of second pivotal Study D961FC00003

A total of 2688 patients were enrolled, 2426 randomised (817 on esomeprazole 40 mg, 804 on esomeprazole 20 mg and 805 on placebo) and 2034 completed (711 on esomeprazole 40 mg, 686 on esomeprazole 20 mg and 637 on placebo).

Subject demographics and baseline characteristics were similar in each group with a mean age of 67.6 years and approximately 35-36% patients older than 70 years. Overall 52.3% of subjects were male. More than 85% of patients had received regular aspirin for at least 4 weeks before randomisation. More than 85% had no previous history of either gastric or duodenal ulcer and more than 90% had no history of erosive oesophagitis. Approximately 10% of patients had duodenal erosions at baseline and 43% had gastric erosions. Findings in the PP set were the same. Approximately 1/3 of patients experienced dyspeptic or GORD symptoms at baseline.

The observed rates for the primary endpoint of peptic ulcer, that is, gastric and/or duodenal ulcer and for the separate secondary endpoints of gastric ulcer and of duodenal ulcer by Week 26 in the ITT set are shown in the Table 8 above.

The absolute risk reduction (ARR) for peptic ulcer in the esomeprazole group 40 mg group was 5.2% (95% CI [3.4%, 7.1%]) versus placebo and the relative risk reduction (RRR) was 79.6%. The ARR for peptic ulcer in the esomeprazole 20 mg group was 5.6% (95% CI [3.7%, 7.4%] versus placebo and the RRR was 84.9%. Both these results were highly statistically significant. A difference in risk reduction between the esomeprazole 20 mg and 40 mg doses was not established.

The secondary efficacy results were generally supportive of the primary efficacy results. There were highly statistically significant reductions in the rates of gastric ulcers and duodenal ulcers, considered separately. Dyspeptic and GORD symptoms, as did upper GI erosions assessed by the RDQ occurred less frequently in patients treated with either esomeprazole 40 mg or 20 mg compared with placebo. Upper GI complications occurred infrequently in all treatment groups and the numbers were too small for any meaningful comparison.

Effect of gender, age, H pylori status and aspirin dose in pivotal Studies D9617C00011 and D961FC00003

The rates of occurrence of peptic ulcers were independent of gender, age (< 65 years versus ≥ 65 years), H. pylori status (negative versus positive) and aspirin dose (75-100 mg versus 101-325 mg).

Safety

A total of 104 healthy subjects were evaluated for safety in the Phase I studies. A total of 3395 patients were included in the safety set from the Phase III studies with 814 having received esomeprazole 40 mg, 1286 having received esomeprazole 20 mg and 1295 having received placebo for a planned duration of 26 weeks. Median exposure was 181 days in all treatment arms.

The rates of any AE, fatal AEs and non-fatal SAEs were all balanced between the esomeprazole 20 mg and placebo treatment arms. There was a slight excess of AEs leading to discontinuation of treatment in the placebo arm (4.3% in esomeprazole 20 mg, 6.0% in placebo) and a very slight excess of related AEs in the esomeprazole 20 mg arm (4.1% in esomeprazole 20 mg and 3.8% in placebo).

The clinical evaluation report (CER) shows the number (%) of patients who had adverse events by System Organ Class in the pooled Phase III safety population (pooled esomeprazole 20 mg versus pooled placebo). These rates were all reasonably well balanced between treatment arms. Interestingly, the rate of gastrointestinal disorders was higher in the esomeprazole 20 mg arm (11.9%) than it was in the placebo arm (11.0%).

The number (%) of patients with the most commonly reported adverse events in decreasing order of frequency in the pooled safety population (pooled esomeprazole 20 mg versus pooled placebo) are described in the CER. The most commonly reported were diarrhoea and upper respiratory tract infection. Rates were reasonably well balanced

between arms. As might have been expected, the rate of abdominal pain upper was less in the esomeprazole 20 mg arm (0.7%) than in the placebo arm (1.8%) and similarly that of dyspepsia was less in the esomeprazole 20 mg arm (0.5%) than in the placebo arm (1.6%). However, it must be observed that the latter two rates were low anyway in the placebo arm. The rates of nausea were almost the same in each arm (1.2% in the esomeprazole 20 mg arm vs. 1.3% in the placebo arm).

In the first pivotal study, D9617C00011, there were 6 withdrawals from the study because of bleeding complications; 4 patients from the placebo group and 2 patients from the esomeprazole 20 mg group. In the second pivotal study, D961FC00003, there were two withdrawals for upper GI complications in the esomeprazole 20 mg group (one haematemesis and one perforation) and two in the placebo group (both melaena). Haematochezia (blood in the faeces) occurred in 7 patients (4 in the esomeprazole 40 mg group and 3 in the esomeprazole 20 mg group). The Delegate made a couple of comments here. Firstly, in reporting these data, the evaluator did not accurately state the study identification numbers (IDs). Therefore, would the sponsor please confirm the various numbers of withdrawals from each of the pivotal studies. Secondly, the Delegate could not find the events of haematemesis or melaena listed as serious AEs. Were these not serious adverse events? Thirdly, the sponsor was asked to please confirm that the case of perforation was that of duodenal perforation reported as a serious adverse event. Fourthly, the sponsor please was asked to clarify the reporting of blood in the faeces. Was this faecal occult blood or frank blood? If the latter was this solely by patient report?

There were no deaths in the Phase I studies. There were a total of 11 deaths in the safety population of the two pivotal Phase III studies. In the first pivotal study, D9617C00011, there were no deaths in the esomeprazole 20 mg group while 2 deaths occurred in the placebo group, one of ischaemic stroke and one of bladder cancer. In the second pivotal study, D961FC00003, 9 patients died during the study, 4 (0.5%) in the esomeprazole 40 mg group, 4 (0.5%) in the esomeprazole 20 mg group and 1 (0.1%) in the placebo group. Five of these deaths in the second pivotal study appeared to be cardiac: 2 in the esomeprazole 40 mg group (MI & sudden death), 2 in the esomeprazole 20 mg group (ACS/cerebral circulatory failure and cardiac arrest). This would give rise to a death rate due to cardiac causes of 4/1613 for esomeprazole (20 or 40 mg) which would be approximately double that of the rate in the placebo group, namely 1/801. The events of ACS and cerebral circulatory failure would appear to have been in the one patient. The sponsor was asked to verify that this was the case. For the safety population overall there were 8 patient deaths due to either a cardiovascular or cerebrovascular cause (Table 22).

Table 22. Deaths

Esomeprazole (20 or 40 mg), n = 2100	Placebo, n = 1295
1 (ACS/cerebral circulatory failure) 1 (cardiac arrest) 1 (cerebrovascular accident) 1 (death, ? unknown cause – Delegate) 1 (myocardial infarction) 1 (sudden death)	1 (ischaemic stroke) 1 (placebo)
Total 6, rate = 6/2100 = 0.29%	Total 2, rate = 2/1295 = 0.15%

No SAEs were reported in the Phase I studies. Non-fatal SAEs by System Organ Class have been discussed above (CER) for the Phase III. Frequencies of these events were similar across treatment groups. Cerebrovascular disorders including cerebral arteriosclerosis, cerebral circulatory failure, cerebral infarction, cerebrovascular accident, cerebrovascular disorder, cerebrovascular insufficiency, ischaemic stroke, transient ischaemic attack and vascular encephalopathy occurred in 10 (0.5%) patients treated with esomeprazole and 2 (0.2%) patients on placebo. The evaluator then made the point that when analysing all adverse events (deaths, non-fatal SAEs and AEs) using the same preferred terms, 11 (0.5%) patients were in the esomeprazole groups and 7 (0.5%) patients in the placebo group. However, the Delegate did not think that it was entirely appropriate to bring together all such events irrespective of degree of seriousness. The Delegate requested that the sponsor provide an analysis of cerebrovascular disorders using these same preferred terms which counts deaths and non-fatal SAEs together and which compares the rate in the subjects taking esomeprazole and those taking placebo. The sponsor was also asked to carry out a similar analysis of cardiovascular disorders which captures all possible preferred terms, that is, one which counts deaths and non-fatal SAEs together and which compares the rate in the subjects taking esomeprazole and those taking placebo.

There were no significant safety signals from either the laboratory findings or from the data set of vital signs and ECG abnormalities.

The most frequent events leading to discontinuation were dyspepsia and abdominal pain. The frequency of adverse events in the gastrointestinal disorders System Organ Class was 1.6% in the pooled esomeprazole 20 mg group and 2.9% in the pooled placebo 20 mg group. Older patients (≥ 65 years) had slightly more adverse events than younger patients.

Risk management plan

A Risk Management Plan (RMP) was evaluated by the RMP evaluator in the Office of Product Review. The RMP evaluator has advised that the submitted RMP is supportive to the application and has recommended that the implementation of the RMP Version 2 dated 09 June 2011 incorporating, where relevant, the sponsor's responses to the TGA's questions, should be made a specific condition of registration, with the following qualification:

It was recommended that the sponsor expand the Australian-specific annex (see *Pharmacovigilance Findings* above). The RMP evaluator asked the sponsor a number of questions including three questions the answers to which have important implications with regard to the satisfactory demonstration of the safety and efficacy of Axanum.

The first of these questions related to the results of two pharmacoepidemiology studies. The first study, D9612N00013 was an osteoporosis/osteoporotic fractures study of the association between acid-suppressing treatment and the risk of hip fractures and falls. The results did not lead to any changes to the safety specifications for either of the components aspirin or esomeprazole or for the combined product and hence no changes are required to the pharmacovigilance or risk minimisation plans. The second study, D9612N00012, examined the potential interaction between clopidogrel and PPIs and was designed to address the separate risks of 2 outcomes, myocardial infarction/coronary heart disease death and upper gastrointestinal bleeding.

The second question concerned the raising in the literature[16] of a possible association between PPIs and cardiovascular risk. The study of Charlot et al 2010, a nationwide cohort study in Denmark based on linked administrative registry data, examined the risk of adverse cardiovascular outcomes related to concomitant use of PPIs and clopidogrel compared with that of PPIs alone in adults hospitalised for myocardial infarction. PPIs appeared to be associated with an increased risk of adverse cardiovascular outcomes after discharge, regardless of clopidogrel use for myocardial infarction. Dual PPI and clopidogrel use was not associated with any additional risk of adverse cardiovascular events over that observed for patients prescribed a PPI alone. There were a number of limitations of the study. The sponsor pointed out that co-prescribing of a PPI is more likely to occur in patients at highest risk of CV events and has been viewed as a marker of worse cardiovascular prognosis. Literature was cited in support of this. The sponsor also noted that recent epidemiological studies had emphasised rigorous control of confounding by indication and channelling bias as well as assessing continuous drug exposure in evaluating any association between drug exposure and outcomes. Again, the sponsor concluded that the results of this study did not necessitate any changes to the pharmacovigilance or risk minimisation plans.

Finally, the sponsor commented that the potential for an increased risk of cardiovascular events during treatment with a PPI including esomeprazole and omeprazole was extensively reviewed by AstraZeneca during the second half of 2007 in response to advisory statements issued by both the US FDA and Health Canada prompted by differences in cardiac event rates reported from 2 small, non-blinded, long-term, clinical studies in patients with gastro-oesophageal reflux disease, comparing anti-reflux surgery with either esomeprazole or omeprazole treatment. The US FDA's preliminary conclusion was that these data did not suggest an increased of heart problems for patients treated with omeprazole or esomeprazole.

The third question concerned the possible increased risk of cardiovascular events in aspirin-treated patients using proton pump inhibitors which had been raised in 2 articles[17]. In the article by Charlot et al 2011, the authors concluded that in aspirin-treated patients with recent MI, concomitant PPI therapy was associated with an increased risk of adverse CV events. The study was performed in a population-based cohort, identified through individual-level linkage of nation-wide registries in Denmark. Once again the sponsor countered by saying that any interpretation of results from observational studies needs consideration of methodological aspects including biases and confounding and pointed out what it saw as limitations of the study. Once again the sponsor concluded that no interaction between low-dose aspirin and PPIs, including esomeprazole, had been established and therefore that no change of the product labelling was warranted. The topic has been addressed in the updated version of the RMP. Although it appears under the heading 'Newly identified safety concerns', it has not, according to the sponsor, been considered as a true safety concern and has not been included as a potential risk. Routine pharmacovigilance activities which include continuous review of in-house data, published literature and external databases as well as risk minimisation activities will be applied. The sponsor ended its answer to this question by pointing out that AstraZeneca has been

[16] Charlot M et al (2010). Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use – A nationwide cohort study, Ann Intern Med 153; 6: 378-386 (21 Sept, 2010)

[17] Charlot, M et al (2011). Proton pump inhibitor use and risk of adverse cardiovascular events in aspirin treated patients with first time myocardial infarction: a nationwide propensity score matched study, BMJ2011;342:d2690doi:10.1136/bmj.d2690
Würtz, M et al, The antiplatelet effect of aspirin is reduced by proton pump inhibitors in patients with coronary artery disease, Heartdoi:10.1136/hrt.2009.181107

requested by the BfArM[18], as a post-approval commitment, perform two pharmacoepidemiological studies. These planned studies are nested case-control studies investigating the potential association between low-dose aspirin and PPIs and the risk of acute MI or death from coronary heart disease. Study proposals are outlined in the updated RMP and the study results were available at the end of 2011.

At its meeting of 4 November 2011, the ACSOM agreed that the two pharmacoepidemiological studies proposed by the sponsor were neither sufficient nor adequate to address the issue of a potential association between concomitant use of low-dose aspirin and PPIs with the risk of acute myocardial infarction or death due to coronary heart disease. The committee advised that concomitant use of PPIs and aspirin may reduce the bioavailability of the latter, resulting in reduced inhibition of platelet aggregation. ACSOM also noted that recent studies, those of Charlot et al 2011 and Würtz *et al* 2010 raise concerns that treatment with PPIs significantly reduces aspirin-induced inhibition of platelet aggregation but that their results were not definitive. Furthermore, at least one of the proposed studies was in patients with a previous ischaemic cerebrovascular or cardiovascular event, that is, in a population taking aspirin for secondary cardiovascular prevention. As noted previously by the Delegate, the use of low-dose aspirin in primary prevention of cardiovascular disease is a frequent prescribing pattern here in Australia.

The RMP evaluator has also made a number of recommendations for amendments to both the Pharmacovigilance Plan and to the PI. All of these recommendations for amendments were endorsed by the Delegate.

Risk-benefit analysis

Delegate considerations

Efficacy

The first point that the Delegate would like to make is that it must not be forgotten that the principal reason someone would be taking the fixed-dose combination Axanum would be for cardiovascular prevention, either primary or secondary. It is a medication intended to be taken for the rest of the patient's life and therefore it must be established beyond all reasonable doubt that the fixed-dose combination has no less efficacy than monotherapy aspirin for the purpose of cardiovascular prevention. The Delegate will return later to this issue.

The first pivotal study, D9617C00011 (ASTERIX), was randomised, double-blind, two-armed, parallel-group, evaluating the effects of esomeprazole 20 mg versus placebo on gastroduodenal lesions, erosive oesophagitis and upper GI symptoms in patients taking low-dose aspirin (75-325 mg daily). The second pivotal study, D961FC00003 (OBERON), was designed to compare the effect of esomeprazole 20 or 40 mg once daily versus placebo on the occurrence of peptic ulcers in patients receiving continuous low-dose aspirin (75-325 mg daily). Treatment with low-dose aspirin had been instituted for primary or secondary prevention of cardiovascular or cerebrovascular thromboembolic events. Thus, it would appear that the population studied in the pivotal Phase III trials was a mixture of people taking aspirin either for primary or secondary prevention. They were not solely taking aspirin for secondary prevention. In Australia, the recommendation for the use of aspirin in cardiovascular prevention is as contained with the *Therapeutic Guidelines Cardiovascular* (2008, version 5), namely, "Aspirin is beneficial if the absolute risk of a major cardiovascular event in the next 5 years is greater than 15%. Use: *aspirin*

[18] Bundesinstitut für Arznemittel und Medizinprodukte, the Federal Institute for Drugs and Medical Devices of Germany, Germany being the Reference Member State in Europe for Axanum

100 to 325 mg orally, daily". To obtain an estimate of the absolute risk of a major cardiovascular event in the next 5 years, one uses a cardiovascular risk assessment tool such as that promulgated by the National Heart Foundation of New Zealand. According to such guidelines the patient population taking aspirin for cardiovascular protection would also be a mixture of people taking aspirin either for primary or secondary prevention.

During the 26-week treatment period in the first pivotal study, gastric ulcer and/or duodenal ulcer occurred in 6.2% of placebo patients and 1.8% of the patients taking esomeprazole 20 mg, with a relative risk reduction of 70% and an absolute risk reduction of 4.4%. The clinical evaluator appears to state that the absolute risk reduction in this study was 3.8%. The sponsor was requested to clarify which is the correct value, 3.8% or 4.4%. In the second pivotal study, the absolute risk reduction (ARR) for peptic ulcer in the esomeprazole group 40 mg group was 5.2% (95% CI [3.4%, 7.1%]) versus placebo and the relative risk reduction (RRR) was 79.6%. The ARR for peptic ulcer in the esomeprazole 20 mg group was 5.6% (95% CI [3.7%, 7.4%] versus placebo and the RRR was 84.9%. Both these results were highly statistically significant. A difference in risk reduction between the esomeprazole 20 mg and 40 mg doses was not established. It is the absolute reduction in risk which is of fundamental importance in any discussion of the efficacy of the fixed-dose combination, not the relative risk reduction.

As noted by the clinical evaluator, the sponsor has claimed that peptic ulcers are a surrogate marker for peptic ulcer complications and cited an extensive literature in support of this. However, as also noted by the evaluator, there was little evidence to support this proposal in the studies presented in the dossier. Peptic ulcer rates were low and complications of ulcer, including bleeding, perforation and obstruction, occurred infrequently in both studies.

Risk reduction for duodenal ulcer was demonstrated formally in one of the pivotal studies, the second D961FC00003. It was assessed apparently as an exploratory endpoint in the first of the pivotal studies, D9617C00011. However, based on the confidence interval calculated for this exploratory endpoint, the risk reduction for duodenal ulcer from this latter study was not shown to be statistically significant. While it was only an exploratory endpoint, the result cannot just be ignored. The Delegate assumed that the risk reduction for the separate endpoint of gastric ulcer was also an exploratory endpoint for this study and that, for it, statistical significance was achieved. The fact that one endpoint achieved statistical significance and one did not does require explanation. The lack of replication of the separate duodenal ulcer endpoint does cast some doubt over the efficacy results as a whole. The Delegate was not convinced by the clinical evaluator's assertion that the indication sought was not for duodenal ulcer but for peptic ulcer. By definition, peptic ulcers include duodenal ulcers and there are only two components to the definition, gastric and/or duodenal. Duodenal ulcers constitute a very important part of the definition.

There was another issue related to the GIT-protective efficacy of the proposed fixed-dose combination which was of concern to the Delegate and it is one stemming from the actual formulation design. The members of the ACPM will remember that quite recently there was a submission from the same sponsor for a fixed-dose combination tablet of naproxen and esomeprazole, namely Vimovo. This modified-release tablet consists of an inner enteric-coated naproxen core and an outer immediate-release film coating containing esomeprazole magnesium. Accordingly, esomeprazole is released from Vimovo in the stomach prior to the dissolution of naproxen in the small intestine. The enteric coating prevents naproxen release at pH levels below 5.5 providing protection against possible gastric toxicity of naproxen. For Axanum, the formulation design is, in effect, the reverse of that for the Vimovo tablet. The aspirin component is immediate-release and the esomeprazole component is enteric-coated, gastrin-resistant. Thus, the initiation of any GIT-protective action of esomeprazole is necessarily delayed and the stomach is left

exposed to any local toxic effect of the aspirin. The Delegate found the reversal somewhat puzzling. Is this particular feature of the design of Axanum something which is an obligatory consequence of the pharmacokinetics of aspirin? If it is not an obligatory consequence, then the Delegate was of the view that it was a design deficiency. The sponsor was requested to comment on this issue.

Finally, with regard to efficacy, what concerns the Delegate was what can only be described as the sleeping issue of the efficacy of this proposed fixed-dose combination for cardiovascular prevention. All through the submission it has been assumed that there will be no less efficacy in this regard compared with the monotherapy low-dose aspirin which the subject is currently taking. One can derive some reassurance from the PD interaction Study D961FC00011 which showed that esomeprazole 20 mg once daily in combination with aspirin 81 mg once daily for 5 days did not have any effects on the platelet effects of aspirin as evidenced by the 'Verify Now Aspirin Test' of platelet aggregation and the serum TXB2. However, this was a small study done in healthy volunteers and not in any relevant target population and the impact of esomeprazole on the anti-platelet effects of aspirin was only shown for the one dose, 81 mg of aspirin, rather than across a range of aspirin doses. What most concerned the Delegate was that most people who take this new fixed-dose combination, should it be registered, will inevitably move from a higher dose of aspirin down to the new dose of 81 mg. They will, in effect, be force-titrated downwards.

The clinical evaluator refers to the fact that in Australia over 70% of aspirin use is in the 81 to 100 mg range. In fact most of this group would be accounted for by people who take the enteric-coated 100 mg tablets for which there is a large range of alternatives on the market. Such 100 mg tablets are not designed to be divided. The only practical way of taking a dose less than 100 mg in Australia would be to divide a 300 mg tablet into halves and then into halves again. It is doubtful that a substantial number of people actually would do this regularly on a long-term basis. It was the Delegate's surmise that the remaining 30% of people on low-dose aspirin would be largely accounted for by those taking a dose of 150 mg daily, that is, taking half a 300 mg tablet daily. Even assuming no interaction at all on the part of esomeprazole, the Delegate was concerned that this forced down-titration of the aspirin dose may have unforeseen consequences in terms of cardiovascular prevention. These concerns are only heightened by the fact that we are dealing with a medication which is intended to be taken for the rest of the life of the patient and by a very large number of patients requiring aspirin for either primary or secondary prevention.

Safety and RMP

As already noted, the Delegate had concerns about possible increased rates of cardiovascular and cerebrovascular events in the esomeprazole arms of the pivotal studies. The Delegate asked the sponsor for clarification of the data.

While aspirin may be used for both primary and secondary prevention in the Australian context, there are still unanswered concerns about the possibility of a PD interaction between aspirin and esomeprazole as well as the Delegate's concerns about the effect on a large, lifelong population basis of any possible effects of the enforced down-titration of the aspirin dose as a result of taking Axanum. The clinical evaluator also commented that the proposed indication is for the prevention of ulcers associated with aspirin use and that the justification for the use of low-dose aspirin should be based on usage guidelines and is the responsibility of the prescriber. The Delegate disagreed with this view of the evaluator. Firstly, the prescription of any medicine by a prescriber is always the responsibility of that prescriber. Axanum is no different from any other prescription medicine in that regard. Secondly, the principal reason someone would be taking this medication, for the rest of his or her life, is for its cardiovascular/cerebrovascular protective efficacy. Cardiovascular efficacy is specifically mentioned in the proposed Indications section. One of the major

problems of this submission, in the view of the Delegate, has been its narrow focus on GIT-protective efficacy.

Finally, there were still unresolved concerns about the newly identified safety concerns of osteoporotic fractures in association with prolonged use of PPIs and of community acquired pneumonia in association with the use of PPIs. These issues were canvassed during the evaluation of the submission for Vimovo (subsequently approved), the fixed-dose combination of naproxen and esomeprazole.

Indication

The clinical evaluator has recommended revision of the wording of the Indications to tighten the target population to those patients "at high risk of peptic ulcer". This amendment would go some way to mitigate the concerns of the Delegate as outlined above. However, these concerns of the Delegate reflect fundamental deficiencies in the data set provided in this submission, deficiencies which cannot be reversed or set aside by a simple tweaking of the indication. It was considered to be a first step however and so, at this stage, the Delegate requested the indication be amended to the following:

> *"Axanum is indicated for patients at high risk of peptic ulcer who require aspirin for the prevention of cardiovascular disease (CVD) in combination with esomeprazole for the prevention of ulcers associated with aspirin use."*

It was also unclear in the indication as to the precise definition of the phrase "for the prevention of cardiovascular disease". Does this term implicitly also capture prevention of cerebrovascular disease or not? Should the indication be re-phrased to reflect more accurately the population(s) studied in the pivotal trials? Both the sponsor and the ACPM were invited to comment on this issue.

Summary

The clinical evaluator acknowledged that the overall benefit risk balance was marginal based on the study data presented. The ARRs, although statistically significant, were generally small percentage reductions in peptic ulcer rates coming off already low rates. The pivotal studies were not powered to detect statistically significant reductions in peptic ulcer complications and for a medicine which is proposed to be taken by a large population for the rest of their lives, the Delegate was of the view that this would be important information to know. In fact what evidence there is, suggests that these pivotal trials did not demonstrate that esomeprazole reduced the risk of clinically meaningful events such as GIT bleeding, perforation or obstruction. The sponsor was asked to address this issue in its pre-ACPM response.

Risk reduction for duodenal ulcer, as a separate endpoint, was demonstrated formally in only one of the two pivotal studies. In the smaller of the pivotal studies, it was only examined as an exploratory endpoint and in this study there was no demonstration of statistical significance.

The Delegate expressed puzzlement at the fact that in Axanum the aspirin component is immediate-release and the esomeprazole component is enteric-coated, the reverse of that for the recently approved Vimovo tablet. In the latter case, evidence of efficacy was based on GIT-protective parameters.

The Delegate was concerned by the implicit forced downward titration of the aspirin dose for anyone changing from their current aspirin monotherapy +/- esomeprazole (or any other PPI) to Axanum. It is uncertain whether, particularly considering the large size of the intended patient population and the intended life-long taking of the product, this may or may not have impacts on rates of cardiovascular and/or cerebrovascular morbidity.

There were concerns about possible increased rates of cardiovascular and cerebrovascular events in the esomeprazole arms of the pivotal studies. In the view of the Delegate, it must be established beyond any reasonable doubt whatsoever that there is no increase in these rates. The sponsor did submit the report of a study in healthy volunteers which demonstrated no PD interaction based on 2 parameters. However, this study was not ideal. It should have been conducted in a relevant target population and should have investigated the possibility of a PD interaction over a range of aspirin doses. There are also concerns that the populations studied in each of the two pivotal studies may not have been comparable in terms of cardiovascular/cerebrovascular risk factors. Two pharmacoepidemiological studies were planned to investigate the possibility of an interaction between low dose aspirin and PPI. The TGA's ACSOM was of the view that such pharmacoepidemiological observational studies are simply not adequate to the task, pointing out that instead prospective, preferably randomised studies were required.

It should be remembered that the option of putting low-dose aspirin with esomeprazole together in free combination is already available to Australian prescribers. While it may not be as convenient a combination to take as the Axanum, the prescriber is forced to review regularly the ongoing need for esomeprazole. The Delegate was of the opinion that it would be negligent to recommend approval for this fixed-dose combination product until all the concerns aired earlier about the efficacy and safety of the fixed-dose combination product have been tested in a clinical outcome study.

There remain the concerns, not fully elucidated, about the association between osteoporotic fractures and long-term use of PPIs and that between community-acquired pneumonia and use of PPIs.

Against this background of numerous unresolved concerns about the efficacy and safety of the combination of aspirin and esomeprazole, the Delegate was of the view that the submission of the sponsor cannot be supported and must be rejected.

The Delegate proposed to **reject** this submission by AstraZeneca Pty Ltd to register Axanum (containing aspirin 81 mg immediate release and esomeprazole 20 mg enteric coated, gastrin resistant pellets) based on the safety and efficacy of the product not having been satisfactorily established for the indication below, for the reasons stated above in the Risk / Benefit Discussion.

> *"For patients who require aspirin and esomeprazole, Axanum is indicated for patients who require aspirin for the prevention of cardiovascular disease (CVD) in combination with esomeprazole for the prevention of ulcers associated with aspirin use."*

The sponsor was asked to address various issues in the Pre-ACPM response including the following:

- With regard to the pivotal studies, the Delegate requested clarification of the numbers of withdrawals, of the events of haematemesis or melaena as serious AEs or not, of the case of perforation and of the reporting of blood in the faeces (haematochezia).
- Clarification that the events of ACS and cerebral circulatory failure were in the one patient.
- The re-analysis of the rates of cerebrovascular disorders and of cardiovascular disorders precisely as requested by the Delegate.
- Clarification of the correct value for the ARR for peptic ulcer in the first pivotal study, 3.8% or 4.4%.
- Confirmation that, in the first pivotal Study D9617C00011, there was a numerically higher number of bleeding events in the placebo plus aspirin arm (4 events) than in the esomeprazole 20 mg plus aspirin arm (2 events) and that, in the second pivotal

Study D961FC00003, there was a higher number of perforation, obstruction and bleeding adverse events in the esomeprazole 20 or 40 mg plus aspirin arms (10 events) than in the placebo plus aspirin arm (2 events). Please provide a break-down summary of these events, by number and type.

- Comment from the sponsor on the formulation design of Axanum versus that of Vimovo.
- Clarification of the precise definition of the phrase, 'for the prevention of cardiovascular disease' with regard to the indication for Axanum.

The ACPM's advice was requested on the following:

- Does the ACPM agree with the Delegate that overall, there are sufficient unresolved doubts and concerns with regard to the efficacy and safety of this fixed-dose combination product of aspirin and esomeprazole to warrant rejection of the application?
- Should this product be approved, does the ACPM endorse the recommendation of the Delegate to amend the wording of the Indications to include the further qualification, "*at high risk of peptic ulcer*", to define more accurately its target population?
- Does the ACPM agree with the Delegate that there is a real danger that patients may be commenced on this fixed-dose combination while they may have upper GI symptoms, in the mistaken belief by the clinician that the esomeprazole component will be protective? Does the ACPM therefore agree with the Delegate that there should be a specific precaution that patients are not to be commenced on this medication until any current upper GI symptoms reported by the patient have been fully investigated? Again the Delegate sees such a precaution as crucial to the safe and appropriate use of this fixed-dose combination.
- Does the phrase 'for the prevention of cardiovascular disease' require any amendment to define more accurately the target population of Axanum

The application was submitted for ACPM advice.

Response from Sponsor

Introduction

AstraZeneca (AZ) concurred with the Clinical Evaluator (CE) that the overall benefit:risk balance of Axanum (aspirin/esomeprazole FDC) is positive and thus approval should be recommended. The positive benefit:risk balance of Axanum is further supported by the EU approval (decentralised procedure, 24 countries, completed July 2011). Since the time of the original filing of Axanum in US, AstraZeneca decided to withdraw the application May 2011 based on commercial considerations. The sponsor did not agree with the Delegate's consideration that there were sufficient unresolved doubts and concerns with regard to the efficacy and safety of Axanum to warrant rejection of the application. The basis for this consideration is discussed further below.

Proposed indication

AZ wished to clarify the Axanum indication being proposed for the ACPM discussions. In accordance with the recommendation of both the CE and Delegate, the sponsor clarified that only patients at risk of developing peptic ulcers should receive this treatment and have subsequently included this within our indication. Likewise, in response to the Delegate's comments to further clarify the term "cardiovascular disease" the sponsor proposed "cardio- and cerebrovascular events". Both of these amendments are in line with the patient populations enrolled within the pivotal studies.

"For patients who require aspirin and esomeprazole

Axanum is indicated for patients at risk of developing peptic ulcers who require aspirin for the prevention of cardio- and cerebrovascular events ~~disease in combination with~~ and esomeprazole for the prevention of ulcers associated with aspirin use."

Proposed precaution

AZ also accepted the Delegate's proposal to include a precaution regarding commencement of therapy in patients with current upper GI symptoms. The following text is proposed:

"Use in patients with upper gastrointestinal symptoms: In patients with upper gastrointestinal symptoms, such symptoms should be clinically assessed and if warranted, should be investigated before treatment with Axanum can be considered. If clinically indicated, testing and treatment for H. Pylori infection should be considered."

Benefit:risk assessment of Axanum

AZ considered that the available data do establish the positive benefit:risk profile for Axanum in the above mentioned indication, as:

- The two pivotal Studies D9617C00011 (Study 011) and D961FC00003 (Study 003) demonstrate that esomeprazole statistically significantly reduced endoscopic ulcers (an acceptable surrogate endpoint affirmed by the November 2010 FDA Advisory Committee [AdComm]) to a clinically meaningful extent regarding absolute risk reduction (ARR) (affirmed by the FDA AdComm and EU approval) in patient at GI risk receiving low-dose aspirin. Furthermore, the observed risk reductions are likely to represent conservative estimates as, for ethical reasons, patients at the highest risk for aspirin-related GI complications were excluded from placebo-controlled trials.
- The long-term safety of esomeprazole has been well established with years of patient exposure with the monoproduct. Whilst the Delegate comments on recent concerns about potential risks from the Vimovo evaluation (which was subsequently approved), the sponsor considered that data from the literature and from AZ's internal databases (including data from clinical studies and spontaneous reports from marketed use) have not given convincing evidence for a causal relationship with esomeprazole use.
- The medical need and benefits of chronic low-dose aspirin for the prevention of cardio- and cerebrovascular events are well established, as well as the need for gastroprotection in patients at upper GI risk. Whilst the Delegate raised concerns regarding a potential interaction between esomeprazole and aspirin, AZ considered that clinical trial, literature and adverse event (AE) assessments do not support this concern, and consequently the efficacy of aspirin in combination with esomeprazole for prevention of CV events would be no less than that of aspirin alone.

Axanum, a FDC of aspirin 81 mg and esomeprazole 20 mg, has been developed for prevention of cardio- and cerebrovascular events in patients requiring continuous low-dose aspirin treatment, and who are in need of prophylaxis against aspirin-associated peptic ulcers.

The medical need and benefits of chronic low-dose aspirin for the prevention of cardio- and cerebrovascular events are well established. The choice of aspirin dose (81 mg once daily) proposed for Axanum is supported by PD and clinical data, by Australian guidelines recommending the use of low-dose aspirin (75-150 mg once daily) for all patients with

coronary heart disease (CHD) or who have experienced stroke [19],[20] (National Heart Foundation (NHF) 2011 Updated Guidelines, National Stroke Foundation (NSF) 2010 Guidelines), and by the worldwide use and approval status (including the EU and the US) of this dose. However, chronic low-dose aspirin therapy causes upper GI symptoms, such as dyspepsia[21], mucosal lesions and peptic ulcers[22], the latter of which may lead in the target population to serious complications such as bleeding, perforation or obstruction[23],[24], [25],[22], [26]. In addition, in consideration of the dose-dependent GI toxicity of aspirin, it is advised to use the lowest dose of aspirin shown to be effective in each clinical setting when a patient is at GI risk[27],[28] further supporting the proposed 81 mg dose proposed for Axanum.

As stated by the CE, "the use of proton-pump inhibitors (PPIs) for the prevention of peptic ulcer in patients receiving low-dose aspirin is widely accepted" and is supported by relevant clinical guidelines based on demonstrated effectiveness of PPI co-therapy for reducing aspirin-associated gastropathy[29],[30]. In accordance with the TGA adopted EU CPMP guidance regarding FDCs[31], Axanum meets the criteria for a FDC product, in which one active (esomeprazole) counteracts "an adverse reaction produced by another one" (aspirin-induced ulcers). This provides the main rationale for the development of an aspirin/esomeprazole FDC.

The clinical efficacy of the esomeprazole 20 mg dose (herein referred to as E20) (in enteric coated pellets) has been conclusively established in clinical trials. In Studies 011 and 003,

[19] NHF 2011 Updated Guidelines. Reducing risk in heart disease. Guidelines for preventing cardiovascular events in people with coronary heart disease. Updated 2011. Developed by the Heart Foundation and Cardiac Society of Australia and New Zealand (CSANZ).
[20] NSF 2010 Guidelines. National Stroke Foundation. Clinical guidelines for stroke management 2010. Melbourne Australia.
[21] Brun J and Jones R (2001). Nonsteroidal anti-inflammatory drug-associated dyspepsia: the scale of the problem. Am J Med 2001;110(1A):12S-13S.
[22] Yeomans ND, Lanas AI, Talley NJ, Thomson AB, Daneshjoo R, Eriksson B, et al. (2005). Prevalence and incidence of gastroduodenal ulcers
[23] ACTIVE Investigators 2009. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360. (Published on line 31March 2009.)
[24] Hallas J, Dall M, Andries A, Andersen BS, Aalykke C, Hansen JM, et al. (2006). Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. BMJ 2006;333(7571):726.
[25] Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al. (1998). Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998; 351: 1755-62.
[26] Serrano P, Lanas A, Arroyo MT, Ferreira IJ. (2002). Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Aliment Pharmacol Ther 2002;16(11):1945-53.
[27] Huang ES, Strate LL, Ho WW, Lee SS, Chan AT. (2010). A prospective study of aspirin use and the risk of gastrointestinal bleeding in men. PloS ONE 2010; 5: e15721. doi:10.1371/journal.pone.0015721
[28] Huang ES, Strate LL, Ho WW, Lee SS, Chan AT. (2011). Long-term use of aspirin and risk of gastrointestinal bleeding. Am J Med 2011;124:426-33.
[29] Abraham NS, Hlatky MA, Antman EM, Bhatt DL, Bjorkman DJ, Clark CB, et al. (2010). ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. Circulation 2010;published online Nov 8, 2010; DOI: 10.1161/CIR.0b013e318202f701.
[30] GESA Guidelines 2009. Gastroenterological Society of Australia. NSAIDs and the gastrointestinal tract. Draft 3rd Edition 2009. Digestive Health Foundation.
[31] CHMP/EWP/240/95 Rev 1 Committee for Medicinal Products for Human use (CHMP). Guideline on clinical development of fixed combination medicinal products.
Available from: URL: http://www.ema.europa.eu/pdfs/human/ewp/024095enfin.pdf

E20 treatment in patients taking low-dose aspirin resulted in endoscopic ulcer (an accepted surrogate endpoint) ARRs ranging from 3.8%-5.6% and relative risk reduction (RRR) of 70%-85%, corresponding to a number-needed-to-treat (NNT) of 16-23 with E20 for 6 months to prevent 1 endoscopic ulcer. Furthermore, these results may represent conservative estimates as, for ethical reasons, patients who were at the highest risk for aspirin-related GI complications could not be enrolled in these placebo-controlled studies. Both the EU (via Axanum approval) and the November 2010 FDA AdComm accepted these results as clinically meaningful.

PPIs, including esomeprazole, are generally well tolerated with a side effect profile similar to placebo[32]. Potential risks associated with chronic PPI use, as raised by the Delegate, may include risk of osteoporotic fractures and community-acquired pneumonia (CAP). However, it is AZ's opinion that data from the literature and from AZ's internal databases (including data from clinical studies and spontaneous reports from marketed use) have not given convincing evidence for a causal relationship between osteoporotic fractures and CAP and esomeprazole use.

The Delegate also raised concerns about possible increased rates of cardio- and cerebrovascular events in the esomeprazole arms in 1 of the 2 pivotal trials (Study 003) and that a potential interaction between esomeprazole and aspirin may lead to decreased CV efficacy of aspirin. This issue has been comprehensively explored using several approaches and no risk identified. Lack of a PK or PD interaction was demonstrated in 2 well designed, randomised, crossover clinical studies (Studies D961FC00001 [Study 001] and D961FC00011, respectively). In addition, literature data support the lack of a PK/PD interaction. Similarly, the results of the 2 recently completed pharmacoepidemiologic studies (Studies D961FN00006 [Study 006] and D961FN00007 [Study 007]) do not indicate any interaction. Finally, analysis of externally adjudicated CV serious adverse effects (SAEs) observed in the pivotal trials [using the FDA recommended Major Adverse Cardiovascular Events (MACE; CV death, MI and stroke] did not indicate an imbalance of CV events and suggested that the numerical difference between the esomeprazole and placebo arms in Study 003 is likely to be attributable to the imprecise rate estimate, which is based on a single MACE event (an unusually low event rate) in the placebo arm.

In addition to the efficacy benefits discussed above, concomitant PPI therapy itself and its use in a FDC may also improve aspirin compliance or prevent discontinuation by reducing dyspepsia and the risk of GI events, ultimately improving CV outcomes, as noted in the ACCF/ACG/AHA 2010 consensus document[29]. High compliance to aspirin treatment is important element of the CV event prevention strategy as demonstrated by increase in CV risk in case of aspirin discontinuation[33]. High compliance with gastroprotective therapy and adherence to prescribed aspirin therapy has been shown to decrease the risk of ulcers in patients receiving chronic NSAID therapy, including low-dose aspirin[34],[35],[36], thus providing a further rationale for the development of an esomeprazole/aspirin FDC. While compliance of the FDC versus individual components was not specifically evaluated in the

[32] Yeomans ND. (2011). Reducing the risk of gastroduodenal ulcers with a fixed combination of esomeprazole and low-dose acetyl salicylic acid. Expert Rev Gastroenterol Hepatol 5:447–55.
[33] Sung JJY, Tsoi KKF,Ma TKW,Yung M-YY, Lau JYW, Chiu PWY. (2010a). Causes of mortality in patients with peptic ulcer bleeding: A prospective cohort study of 10,428 cases. Am J Gastroenterol 2010;105:84-9.
[34] Duh MS, Gosselin A, Luo R, Lohoues H, Lewis BE, Crawley JA. (2009). Impact of compliance with proton pump inhibitors on NSAID treatment. American Journal of Managed Care 2009;15(10):681-8.
[35] Sturkenboom MCJM, Burke TA, Tangelder MJD, Dieleman JP, Walton S, Goldstein JL. (2003). Adherence to proton pump inhibitors or H2-receptor antagonists during the use of nonsteroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2003;18:1137-47.
[36] Sung JJ, Lau JY, Ching JY et al. (2010b). Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. Ann. Intern. Med. 152(1), 1–9 (2010).

Axanum program, the CE also supported the compliance benefits stating that there is "strong literature support for increased compliance with FDC" and "it is possible that increased compliance with aspirin in the FDC might lead to a significant reduction in CV events in patients receiving aspirin for prevention".

In summary, AZ considered that the gastroprotection demonstrated in Studies 011 and 003, combined with the overall safety profile of esomeprazole alone and with aspirin, and the weight of evidence regarding CV safety of esomeprazole in combination with low-dose aspirin, establish the positive benefit:risk profile for Axanum in the proposed indication. With an expected 0.5%-1% annual incidence of GI complications among chronic aspirin users and higher in high-risk patients[37], gastroprotection has the potential to confer great benefit in patients at GI risk. These benefits have important public implications given the number of patients at GI risk among Australians taking aspirin for prevention of cardio- and cerebrovascular events, and the severe consequences of upper GI bleeding and noncompliance to aspirin treatment in CHD patients. The sponsor therefore believed that Axanum should be recommended for approval.

The remainder of this response provides greater detail on specific issues raised by the Delegate.

Issues related to gastroprotective efficacy

The Delegate raised concerns about the GI endpoints in the pivotal trials, including adequacy of peptic ulcer as a surrogate marker for GI complications, clinical meaningfulness of the efficacy results and lack of clinically meaningful reductions in GI complications seen in the trials. The gastroprotective efficacy of esomeprazole in patients taking low-dose aspirin was demonstrated in Studies 011 and 003, in which treatment with E20 resulted in an ARR of 3.8-5.6% (see Table 23)(E40 was also efficacious in Study 003, not shown in table) and reduced endoscopic peptic ulcers by 70-85% (RRR). The corresponding NNT for E20 treatment for 6 months to prevent 1 endoscopic ulcer were 23 (95% CI 14.2-55.8; Study 011) and 16 (95% CI 11.9-23.6; Study 003). These results are further supported by the secondary endpoints, including the individual rates of gastric and duodenal ulcers (see Table 23), and upper GI symptoms.

[37] Bhatt DL, Scheiman J, Abraham NS, Antman EM, Chan FK, Furberg CD, et al. (2008). ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation 2008;118:1894-909.

Table 23.

Cumulative proportion of patients with peptic, gastric and duodenal ulcers by Week 26, ITT population

Statistic	Study 011		Study 003*	
	E20 n=493	Placebo n=498	E20 n=804	Placebo n=805
Peptic ulcer				
Life table estimate [95% CI]	1.8% [0.6%-3.1%]	6.2% [3.9%-8.5%]	1.1% [0.3%-1.9%]	7.4% [5.5%-9.3%]
Observed response rate [95% CI]	1.6% [0.7%-3.2%]	5.4% [3.6%-7.8%]	1.0% [0.4%-2.0%]	6.6% [5.0%-8.5%]
ARR [95% CI]	3.8% [1.5%-6.1%]		5.6% [3.7%-7.4%]	
RRR	70.1	.	84.9	.
Log rank p-value (vs placebo)	0.0005	.	<0.0001	.
Gastric ulcer				
Life table estimate [95% CI]	1.4% [0.3%-2.5%]	4.5% [2.5%-6.5%]	0.8% [0.2%-1.5%]	4.7% [3.1%-6.2%]
Observed response rate [95% CI]	1.2% [0.4%-2.6%]	3.8% [2.3%-5.9%]	0.7% [0.3%-1.6%]	4.1% [2.8%-5.7%]
ARR (95% CI)	2.6% [0.7%-4.5%]		3.4% [1.9%-4.8%]	
RRR	68.1	.	81.8	.
Log rank p-value (vs placebo)	0.0046	.	<0.0001	.
Duodenal ulcer				
Life table estimate [95% CI]	0.5% [-0.2%-1.1%]	1.8% [0.6%-3.1%]	0.3% [-0.1%-0.6%]	3.1% [1.8%-4.4%]
Observed response rate [95% CI]	0.4% [0.0%-1.5%]	1.6% [0.7%-3.1%]	0.2% [0.0%-0.9%]	2.7% [1.7%-4.1%]
ARR [95% CI]	1.2% [-0.0%-2.4%]		2.5% [1.3%-3.7%]	
RRR	74.7	.	90.9	.
Log rank p-value (vs placebo)	0.0431	.	<0.0001	.

Data derived from Summary of Clinical Efficacy, Table 9 & consistent with draft PI (*Esomeprazole 40mg data for Study 003 not provided within this response).

ITT Intention to treat; E20 Esomeprazole 20 mg once daily; ORR Observed response rate; ARR Absolute risk reduction; RRR Relative risk reduction; CI Confidence intervals.

Peptic ulcer as surrogate marker for upper GI complications

Endoscopic upper GI ulcers as the primary endpoint in support of efficacy of gastroprotective agents in patients receiving NSAIDs (including aspirin) have been accepted previously by various Regulatory Authorities, including the TGA (such as Nexium and Vimovo). AZ considers that endoscopically diagnosed ulcers are a biologically plausible surrogate endpoint for aspirin-associated upper GI bleeding, as bleedings to a high degree come from gastric/duodenal ulcerations. Gastric and duodenal ulcerations are also in the common shared pathway whether the bleeding is evoked by NSAID/aspirin´s ulcerogenic effect on the mucosa or by its anti-aggregation effect on platelets. In further support of AZ's consideration, the adequacy of endoscopic ulcers as a primary efficacy endpoint in this setting was discussed at the above-mentioned November 2010 FDA GI AdComm, which also concluded that this surrogate marker was an acceptable primary endpoint. The FDA AdComm also affirmed that decreases in endoscopic ulcers are paralleled by decreases in upper GI complications.

Clinical meaningfulness of absolute endoscopic ulcer reduction in pivotal trials

The November 2010 FDA AdComm also discussed whether the 3% ARR in endoscopic ulcers in patients taking chronic low-dose aspirin over 6 months, as demonstrated in the Axanum pivotal Study 011, as an example. The AdComm concluded that this result would be clinically meaningful because the large number of patients taking aspirin for the prevention of CV events translates a modest ARR into a meaningful clinical benefit. This was also the view of the CE who considered the efficacy results to be acceptable and subsequently recommended approval. The Committee also noted that risk stratification must be considered, as the anticipated ARR is dependent on the existing risk/numbers of events in the population treated. These considerations further support AZ view that use of esomeprazole should be considered for aspirin users at increased risk for aspirin-associated GI complications.

Duodenal ulcers

The Delegate acknowledged that the risk reduction for duodenal ulcer as an individual endpoint was formally demonstrated in Study 003 (see Table 23). However the Delegate did query the Study 011 result. AZ acknowledged that the duodenal ulcer ARR 95% CI, based on the crude rates, did not exclude 0 in Study 011 [see section '*Other items*']. However, the primary efficacy variable was time to occurrence of peptic ulcer (gastric

and/or duodenal ulcer) and use of the log-rank test and Kaplan-Meier (KM) estimates were pre-specified. Evaluating duodenal ulcers in the manner pre-specified for peptic ulcers (in which the time to an ulcer is taken into consideration and patients who discontinue from the study have the same probability of having an ulcer as the patients remaining in the study) yields a p- value of 0.0431 (see Table 23). The sponsor therefore considers that these results, taken together with those from Study 003, indicate replication of efficacy with respect to the risk reduction even for duodenal ulcers.

Upper GI complications as endpoints in the pivotal trials

The primary objective of the 2 pivotal studies was to evaluate the effect of 26 weeks treatment with esomeprazole versus placebo for reducing the risk of the accepted surrogate endpoint, peptic ulcers, in patients taking low-dose aspirin. The studies were not designed nor powered to evaluate ulcer complications and complications were not included as an efficacy variable in the studies. In Study 011, all safety reports were evaluated in order to cover potential upper GI complications. In Study 003, GI complications were pre-defined (hematemesis, melena, hematochezia, perforation, gastric outlet obstruction and "other"). In total, there were numerically more upper GI complications in the placebo groups (7 events/554 exposure years) compared to the 2 esomeprazole dose groups (5 events/957 exposure years) in Studies 011 and 003 combined. However, the numbers of ulcer complication were too small to draw any firm conclusions. The NNT to prevent upper GI complications over 1 year with esomeprazole in patients on aspirin from 2 studies reported in the literature were 13 and 7,[38],[39], respectively). Note, those studies have a different design and treatment regimen compared with Study 011 and Study 003, and they included only high risk patients, that is, patients who had experienced a recent gastric and/or duodenal ulcer bleeding. As stated, the November 2010 FDA AdComm affirmed that decreases in endoscopic ulcers, as seen in the pivotal trials, are paralleled by decreases in upper GI complications.

Issues relating to CV event prevention by aspirin

Choice of aspirin dose in the FDC

The Delegate expressed a concern that patients who take the FDC are likely to be moved from a higher dose of aspirin to a new dose of 81 mg ("force-titrated downwards"), with potential consequences for CV prevention. AZ did not consider that the change in aspirin dose resulting from a switch to the FDC has clinical relevance from the CV perspective. The bulk of PD and clinical data support the preventive effect on CV event of aspirin in doses <100 mg and suggest that there is no difference in CV prevention efficacy between aspirin in the range 75-100 mg versus 100-325 mg daily[40],[41],[42],[43], [44]). In contrast, several studies

[38] Chan FK, Ching JY, Hung LC, Wong VW, Leung VK, Kung NN, et al. (2005). Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med 2005;352(3):238-44.
[39] Lai KC, Chu KM, Hui WM, Wong BC, Hung WK, Loo CK, et al. (2006). Esomeprazole with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. Clin Gastroenterol Hepatol 2006;4(7):860-5.
[40] Antithrombotic Trialists' Collaboration 2009. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. Lancet 2009;373:1849-60.
[41] Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, et al. (2003). Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to Prevent Recurrent Events (CURE) study. Circulation 2003;108(14):1682-7.
[42] Berger JS, Brown DL, Becker RC. (2008). Low-dose aspirin in patients with stable cardiovascular disease: A meta-analysis. Am J Med 2008;121:43-9.
[43] Campbell CL, Smyth S, Montalescot G, Steinhubl SR. (2007). Aspirin dose for the prevention of cardiovascular disease: a systematic review. JAMA 2007;297(18):2018-24.

have demonstrated an increased incidence of GI bleeding with an increased aspirin dose[41,43,37,45,46,47]. Furthermore, there is no PD dose-response relationship regarding antiplatelet inhibition for the aspirin dose range of 75-325 mg daily[48]. In consideration of the dose-dependency aspirin related GI toxicity, physicians are encouraged to use the lowest dose of aspirin shown to be effective in each clinical setting[27,28]. International and Australian guidelines regarding aspirin doses for prevention of cerebro- and cardiovascular events[19, 20], support use of an aspirin dose range of 75-150 mg daily, for long-term prevention of serious vascular events in patients with CHD, after taking into account both the lack of increased efficacy and increased side effects at higher doses. Thus, a change in aspirin dose within the dose range of 75-150 mg would not be clinically relevant and the FDC aspirin dose of 81 mg is therefore considered generally suitable for all patients. The aspirin dose 81 mg has been approved in many countries including USA and EU and it has been one of the most prevalent doses used world-wide; Axanum with this aspirin dose has now also been approved in the EU.

PK, PD, and pharmacoepidemiologic evaluation of a potential esomeprazole/aspirin interaction

PK and PD data - target population and dose selection

The Delegate commented that the results of submitted PD interaction Study (D961FC00011) provide reassurance regarding a potential interaction but expressed concerns regarding the target population and study drug doses used. Both the submitted PK (Study 001) and PD (Study D961FC00011) interaction studies, were conducted in accordance with the TGA-adopted EU guideline[49] and FDA requirements for study populations within clinical interaction studies. Healthy volunteers were preferred in the studies to avoid interference from disease processes or other drugs commonly used in the patient population, and because the accepted endpoints (inhibition of platelet aggregation and suppression of TXB2 production) are measurable in healthy volunteers. To approximate the age of the target patient population, the protocol specified that ≥50% of subjects should be aged 50-75 years; and in fact, 67% were within 50-75 years. The possible effects of concomitant administration of esomeprazole on the aspirin PD effect in healthy volunteers are expected to be similar to the target patient population.

The doses of study drugs used in the PK study (Study 001) were, based on the TGA-adopted EU and FDA regulatory guidance for conduct of drug interaction studies, the highest proposed therapeutic doses in the Axanum development program (325 mg aspirin/40 mg esomeprazole). AZ considered that the results demonstrating lack of PK interaction applicable for other therapeutic doses of the 2 drugs for the following reasons: (1) aspirin and esomeprazole have completely different metabolic/elimination pathways.

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[44] Steinhubl SR, Bhatt DL, Brennan DM, Montalescot G, Hankey GJ, Eikelboom JW, et al. (2009). Aspirin to prevent cardiovascular disease: The association of aspirin dose and clopidogrel with thrombosis and bleeding. Ann Intern Med 2009;150:379-86.
[45] Aronow HD, Califf RM, Harrington RA, Vallee M, Graffagnino C, Shuab A, et al. (2008). Relation between aspirin dose, all-cause mortality, and bleeding in patients with recent cerebrovscular or coronary ischemic events (from the BRAVO trial). Am J Cardiol 2008;102(10):1285-90.
[46] Patrono C, Baigent C, Hirsch J, Roth G. (2008). American College of Chest Physicians. Antplatelet drugs: American College of Chest Physiscians evidence based clinical practice guidelines (8th edition). Chest 2008;133(6 suppl):199S-233S.
[47] Weil J, Colin-Jones D, Langman M, Lawson D, Logan R, Murphy M, et al. (1995). Prophylactic aspirin and risk of peptic ulcer bleeding. BMJ 1995;310(6983):827-30.
[48] Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. (2005). Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med 2005;353(22):2373-83.
[49] CPMP/EWP/560/95. Committee for Proprietary Medicinal Products (CPMP). Note for guidance on the investigation of drug interactions. Available from: URL: http://www.tga.gov.au/pdf/euguide/ewp056095en.pdf

Metabolic interaction should have been captured by PK study, which used repeated administration of the highest proposed doses of both drugs; (2) Potential interaction at an absorption level due to increased intragastric pH by esomeprazole (possibly affecting aspirin bioavailability) should also have been detected using the highest esomeprazole 40 mg dose; (3) A well-known linear dose-exposure relationship of aspirin within a wide dose range implies that the same results can be expected with a lower dose, that is, 81 mg. In the PD interaction study (D961FC00011) the 81 mg aspirin and 20 mg esomeprazole doses were selected because the content in the FDC, combination product (aspirin 81 mg/esomeprazole 20 mg). Theoretically, because of different mechanisms and sites of actions for the 2 compounds, any PD interaction should primarily be due to a PK (including absorption) effect unless an unknown mechanism of esomeprazole that would affect platelet aggregation directly would exist. A negative result for a PD interaction study should therefore confirm the conclusion drawn from the PK interaction study that there is no clinically relevant interaction between aspirin and esomeprazole.

Supporting the results of the PK/PD data are results from 4 published randomised, crossover design studies[50],[51],[52],[53] evaluating interaction between PPIs (omeprazole, lansoprazole, and pantoprazole) and aspirin (2 of which were in CV patients). These studies provide consistent, supportive evidence for a lack of PK or PD interaction between concomitant PPI treatment and aspirin. In contrast, the results of 1 recent case control study[54] suggested a possible interaction, although the shortcomings in design should be noted (non-randomised, non-crossover design, no baseline values, unclear methodology and high variability in data) as well as the fact that TXB2 was still suppressed to a clinically adequate extent (indicating adequate therapeutic effect) in both treatment arms. In addition to these data, published results of a recent large randomised, controlled trial (COGENT[55]) comparing a fixed combination of clopidogrel 75 mg and omeprazole 20 mg versus clopidogrel alone and where all patients received aspirin, also failed to provide any evidence for a clinically relevant CV risk from combined clopidogrel and omeprazole when given together with aspirin in patients with CHD.

Pharmacoepidemiology data

The Delegate stated that a pharmacoepidemiology study17 raised concerns that PPIs may reduce aspirin-induced inhibition of platelet aggregation. Two nested case-control studies (Studies 006 and 007; as discussed within the updated Axanum RMP) investigating the association between low-dose aspirin and PPIs and risk of acute MI or CHD death, were designed to address design limitations (such as potential selection bias, inaccurate classification of ASA and PPI exposure, lack of information about CV risk profile and issues of statistical validity) of the Charlot et al (2011) study[17] The Delegate has reiterated criticisms raised by the Advisory Committee of the Safety of Medicines (ACSOM) in relation to the RMP evaluation, that "these proposed pharmacoepidemiologic studies were

[50] Adamopoulus AB, Sakizlis GN, Nasothiomioiu EG, Anastasopoulu I, Anastasakou E, Kotsi P, et al. (2009). Do proton pump inhibitions attenuate the effect of aspirin on platelet aggregation? A randomized crossover study. Cardiovasc Pharmacol 2009;54:163-8.
[51] Kasprzak M, Kozinski M, Bielis L, Boinska J, Plazuk W, Marciniak A, et al. (2009). Pantoprazole may enhance antiplatelet effect of enteric-coated aspirin in patients with acute coronary syndrome. Cardiol J 2009;6:535-44.
[52] Inarrea P, Esteva F, Cornudella R, Lanas A. (2000). Omeprazole does not interfere with the antiplatelet effect of low-dose aspirin in man. Scand J Gastroenterol 2000;35:242-6.
[53] Nefesoglu FZ, Ayanoglu-Dulger G, Ulusoy NB, Imeryuz N. (1998). Interaction of omeprazole with enteric-coated salicylate tablets. Int J Clin Pharmacol Ther 1998;36:549-53.
[54] Würtz M, Grove EL, Kristensen SD, Hvas A-M. (2010). The antiplatelet effect of aspirin is reduced by proton pump inhibitors in patients with coronary artery disease. Heart 2010;96:368-71.
[55] Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, et al for the COGENT investigators. (2010). Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med. 2010 Nov 11;363(20):1909-17.

not sufficient or adequate to address the issue of a potential interaction." The ACSOM criticism appeared to relate at least in part to studying a target population of secondary and not primary prevention patients. However, there is no scientific rationale (nor any data) to support any difference between primary and secondary prevention patients regarding a hypothetical interaction between aspirin and PPIs. Both studies were performed among first time users of low-dose aspirin using the UK primary care databases (THIN and GPRD). These studies have recently completed, with both studies concluding that there was no increased risk of MI/CHD deaths when PPI were prescribed concomitantly when the treatment with low-dose aspirin was initiated, and thus the results were not in line with those of Charlot et al (2011)[17].

In summary, the results from the PK, PD and pharmacoepidemiology studies combined with the clinical (CV) data from the esomeprazole/aspirin development program, support the lack of interaction between esomeprazole and aspirin with regard to CV prevention by aspirin.

Cardio and cerebrovascular events in the pivotal trials

The Delegate requested an analysis of CV events that captures deaths and non-fatal SAEs together and compares the rate in subjects taking esomeprazole and those taking placebo. AZ undertook an analysis in which all CV SAEs were classified by blinded adjudication and analyzed for Studies 011 and 003. FDA guidance on evaluating CV outcomes[56] recommends primary reliance on the MACE endpoint, comprising the components CV death, MI or stroke. MACE is considered to be more objective and less subject to bias than endpoints such as coronary revascularisation or hospitalisation due to unstable angina. Therefore, MACE events have been considered foremost in the present analysis, followed by consideration of other serious thrombotic/ischemic and any serious CV event. To classify events as accurately as possible, AZ subjected all reported SAEs to a blinded, independent adjudication procedure. Available clinical information for SAEs was redacted for information related to treatment assignment and given to an external cardiologist for blinded review. A listing of all SAEs with preferred terms (PTs) and adjudication category for the 2 trials was included with this response. Results are presented in Table 24. MACE events confirmed by adjudication were infrequent, leading to imprecise event rate estimates. The MACE rate was higher with placebo compared with esomeprazole in Study 011 while the opposite pattern was observed in Study 003. When the studies were taken together, the MACE rate was similar with esomeprazole and placebo. A similar pattern was observed for ischemic/thrombotic CV SAEs and for any CV SAE.

The analysis in Table 24 takes into account the PTs related to cerebrovascular disorders listed by the Delegate (cerebral arteriosclerosis, cerebral circulatory failure, cerebral infarction, cerebrovascular accident, cerebrovascular disorder, cerebrovascular insufficiency, ischemic stroke, transient ischemic attack [TIA], and vascular encephalopathy); all SAEs in the pivotal trials with their adjudication result are in the attached listing. Note that CV deaths in the MACE endpoint include all cardio- and cerebrovascular deaths and thus would include any fatal SAEs that were reported as 1 of the specified cerebrovascular PTs (if confirmed as a CV death by adjudication). Adjudication results for events of these cerebrovascular PTs were as follows: CV death (3 events; 2 in the E20 group, 1 in the placebo group); stroke (6 events, 4 in the E20 group, 1 in the E40 group and 1 in placebo); TIA (2 events; both in the E20 group; note that there was 1 additional event of TIA identified by adjudication in the placebo group that had been previously classed as non-CV, PT carotid arteriosclerosis, which is now present in Table 24, whereas 1 event with PT TIA in the E20 group was classified by the adjudicator as

[56] Joffe HV, Parks MH, Temple R. (2010). Impact of cardiovascular outcomes on the development and approval of medications for the treatment of diabetes mellitus. Rev Endocr Metab Disord 2010;11:21-30.

"unable to classify as CV/non-CV"); Unable to classify as CV/non-CV (2 events; 1 in the E20 group, 1 in the placebo group).

Table 24.

N and 6-month event rate of CV SAEs classified by blinded adjudication, Studies 011 and 003, safety population

	Study 011		Study 003			Study 011 and 003	
	E20	Placebo	E40	E20	Placebo	E40/20	Placebo
n	**487**	**493**	**814**	**799**	**801**	**2100**	**1294**
Exposure, patient years	**222**	**210**	**372**	**362**	**344**	**957**	**554**
CV death, n	0	1	2	3	1	5	2
Myocardial infarction, n	0	3	0	1	0	1	3
Stroke, n	1	1	1	3	0	5	1
MACE, n	**1**	**5**	**3**	**7**	**1**	**11**	**6**
6 months event rate, %	**0.23**	**1.19**	**0.40**	**0.97**	**0.15**	**0.57**	**0.54**
Unstable angina, n	4	4	5	2	3	11	7
Transient ischemic attack, n	1	0	0	1	1	2	1
Other ischemic/ thrombotic, n	0	0	6	0	2	6	2
Any isch/ thromb SAE, n	**6**	**9**	**14**	**10**	**7**	**30**	**16**
6 month event rate, %	**1.35**	**2.14**	**1.88**	**1.38**	**1.02**	**1.57**	**1.44**
Non-isch/ thromb SAE, n	5	7	3	3	3	11	10
Any CV SAE, n	**11**	**16**	**17**	**13**	**10**	**41**	**26**
6 month event rate, %	**2.48**	**3.80**	**2.28**	**1.79**	**1.45**	**2.14**	**2.35**

MACE major adverse CV event (MI, stroke, CV death); isch/ thromb ischemic/ thrombotic. CV events are hierarchical, with the most severe event listed first. Patients with more than 1 CV SAE are counted once in the most severe category. Any ischemic/thrombotic SAE (MACE, unstable angina, transient ischemic attack, other ischemic/thrombotic SAE), Any CV SAE (Any ischemic/thrombotic SAE, Non-ischemic/thrombotic SAE). NOTE: The category of "CV death" in the MACE endpoint comprises all cardio- and cerebrovascular deaths.

AZ examined baseline CV characteristics of the 2 pivotal trial populations based on Framingham risk criteria[57] and aspirin use and concluded that the 2 study populations were similar in these respects despite some differences in inclusion criteria*. Despite this similarity, placebo event rates differed in the studies, likely due to unstable rate estimates because of small numbers of events. Compared with event rates in published aspirin trials of prespecified CV endpoints in primary and secondary CV prevention populations (separately or mixed, like Studies 011 and 003) (that is, Antithrombotic Trialists' Collaboration 200940, CHARISMA, ASCOT), numbers of CV events among patients receiving aspirin alone (placebo) in the pivotal trials were extremely low in Study 003. Therefore, the numerical difference in CV event rates between esomeprazole and placebo in Study 003 may be attributable to the imprecise rate estimate, which is based upon a single MACE event (resulting in an unusually low event rate in this population) in the placebo arm.

Need for large CV outcomes trial

The CE concluded that a large clinical outcomes trial with esomeprazole in patients taking esomeprazole and aspirin (81 and 325 mg) was not necessary. However, the Delegate disagreed with this view and requested that a large clinical outcomes trial be performed to evaluate the efficacy of esomeprazole in reducing GI complications in individuals taking low-dose aspirin for secondary prevention, and that it be powered to detect an adverse impact of the addition of E20 to aspirin 81 and 325 mg on cardio- and cerebrovascular events. Furthermore, the adequacy of the endoscopic endpoint as a surrogate for GI events was affirmed by the November 2010 FDA AdComm, obviating the need for a GI outcomes study.

AZ consider that the adjudicated CV events data from the esomeprazole/aspirin development program (refer above) and of post-marketing AE reports do not indicate an imbalance of CV events requiring evaluation in a CV outcomes trial. Moreover, consideration of a hypothetical non-inferiority study design evaluating the effect of

[57] The Framingham Risk Score is used to estimate the 10-year cardiovascular risk of an individual. The Framingham Risk Score is based on data obtained from the Framingham Heart Study.

esomeprazole in patients taking low-dose aspirin for secondary prevention of MACE raises ethical and feasibility issues. Statistical considerations of published CV trial data indicate a required sample size ranging from 143,000-556,000, which is clearly not feasible. An ethical difficulty when conducting such a CV outcome study is that the efficacy of PPI treatment has been established for GI protection in patients taking aspirin for cardioprotection. Guideline recommendations for PPI treatment would likely impede ethics committee approvals and investigators' participation. A second ethical issue in a CV outcomes study (planned 4-year duration) is the competing risk of GI AEs. Based on data from COGENT[55], a statistically significant difference in GI bleeds between treatments would be anticipated by 3 months, likely leading to termination of the study by a Data Safety Monitoring Board during recruitment. The anticipated excess in GI bleeding calls into question the appropriateness of initiating such a study due to lack of equipoise for GI complications and subjecting patients to risk in a study with low probability of completion.

In summary, review of adjudicated CV events in the esomeprazole/aspirin development program and of postmarketing AE reports does not indicate an imbalance of CV events requiring evaluation in a CV outcomes trial. Further, due to the ethical considerations described above, anticipated high rate of crossover to open-label PPI and high dropout rate among placebo-allocated patients, and the non-feasibility of conducting a 143,000-556,000 patient study that runs counter to current guidelines, AZ's position was that initiation of an outcomes study was not justifiable.

Additional safety concerns raised within the Vimovo submission

The Delegate provided comment on 2 concerns raised during the Vimovo evaluation relating to a potential increased risk of osteoporotic fractures and CAP in association with use of PPIs. AZ have addressed both these concerns within the Vimovo submission, which was subsequently approved by the TGA. There are some epidemiologic data suggesting that long-term PPI use may be associated with an increased risk for osteoporosis-related fractures and CAP. However, regarding osteoporosis-related fractures; no consistent association between PPI use and osteoporotic fractures or accelerated bone mineral density loss has been established in observational studies and no pathophysiological mechanisms have been identified that could unequivocally explain a hypothetical increased risk of osteoporotic fractures in PPI users. Finally, no support for an association between osteoporotic fractures and PPI use from clinical study biomarker or AE data has been identified (LOTUS study, CSR D9612C00003, esomeprazole long-term randomised controlled clinical study). With regard to CAP, published observational studies have shown contradictory results. Furthermore, an analysis of pooled data from AZ-sponsored studies comparing esomeprazole with placebo[58] did not support a causal relationship between esomeprazole treatment and increased risk of pneumonia. Similarly, a meta-analysis of randomised controlled clinical trials and observational studies failed to show a conclusive association between PPIs and respiratory infections and CAP[59],[60].

In conclusion, it is AZ's opinion that data from the literature and from AZ's internal databases (including data from clinical studies and spontaneous reports from marketed use) have not given enough evidence for a causal relationship between either osteoporosis/osteoporotic fractures or CAP and the use of esomeprazole.

[58] Estborn L, Joelson S. (2008). Occurrence of community-acquired respiratory tract infection in patients receiving esomeprazole: retrospective analysis of adverse events in 31 clinical trials. Drug Saf 2008;31:627-36.
[59] Sultan N, Nazareno J, Gregor J. (2008). Association between proton pump inhibitors and respiratory infections: a systematic review and meta-analysis of clinical trials. Can J Gastroenterol. 2008;22:761-6.
[60] Johnstone J, Nerenberg K, Loeb M. (2010). Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia. Aliment Pharmacol Ther. 2010;31:1165-77. Epub 2010 Mar 4.

Other issues

The Delegate requested clarification of the following issues: [Responses have also been presented in the sections "*Cardio- and cerebrovascular events in the pivotal trials*" and "*Proposed indication*".]

With regard to the pivotal studies, the Delegate has requested some clarification regarding GI complications.

For Study 003 signs of GI complications were also collected from the CRF called GICOMP, where the complications were defined prospectively (hematemesis, melena, hematochezia, perforation, gastric outlet obstruction and other) using tick boxes. Some of the GI complications were captured only from the tick boxes on this page and were not reported as AEs. This, together with the fact that 1 event of melena was reported as a non-serious AE, explains why the requested events haematemesis and melena were not found in the SAE table discussed by the Delegate. See response below for further details on how GI complications were collected in the 2 trials.

Withdrawals of events bleeding / upper GI complications

In Study 011, there were 6 withdrawals due to events of bleeding/upper GI complications (4 placebo patients, 2 E20 patients). These included the following: (E20 patient) unconsciousness associated with a GI bleed (assessed to have been caused by diverticulitis) PT Diverticulitis (E20 patient) rebleeding from a gastric leiomyoma, PT Leiomyoma (placebo patient) severe hemorrhagic gastritis, PT Gastritis hemorrhagic (placebo patient) Mallory-Weiss (MW) with oozing hemorrhage PT M-W syndrome (placebo patient) gastric ulcer hemorrhage PT Gastric ulcer hemorrhage (placebo patient) progressive drop in Hb PT Hb decreased.

In Study 003, there were 4 withdrawals due to events of hematemesis, melena, perforation (2 placebo patients and 2 E20 patients). These included the following: (E 20) hematemesis (not reported as AE see above) (E20) perforation, PT duodenal perforation (SAE) (placebo group) melena PT melena (non-serious AE) (placebo group) experienced melena (not reported as AE, only on CRF page, see explanation above)

Perforation case

AZ confirms that the event perforation reported as a GI complication is the same case as reported as SAE for patient a patient from the E20 group.

Reporting of blood in faeces. Was this faecal occult blood or frank blood. If the latter, was this solely by patient report?

The patients were questioned by the investigator if they had experienced any AEs (and in Study 003, additionally if they had experienced any signs of prespecified GI complications including hematochezia). The investigator then made a decision on how to classify the findings.

Clarification that the events of ACS and cerebral circulatory failure were in the one patient.

AZ confirmed that these events occurred in 1 patient; 51 days after start of study drug the subject developed renal insufficiency (assessed as non-SAE by investigator) and ACS. The ECG showed no signs of MI. 55 days after start of investigational product and 4 days after stop of study drug, the subject had a cerebral accident and died the same day. Probable cause of death was central breath paralysis due to cerebral insult.

Clarification of the correct value for the ARR for peptic ulcer in Study 011 (3.8% or 4.4%)

Both values are correct. The ARR value 4.4% is calculated from the 26-week KM life-table estimates (1.8% for E20 and 6.2% for placebo) and the ARR value 3.8% is calculated from the observed crude rates (1.6% for E20 and 5.4% for placebo [see Table 23]). The KM estimates was the pre-specified primary efficacy analysis.

Confirmation that, in Study 011, there was a numerically higher number of bleeding events in the placebo plus aspirin arm (4 events) than in the E20 + aspirin arm (2 events) and that, in Study 003, there was a higher number of perforation, obstruction and bleeding AEs in the E20 or E40 + aspirin arms (10 events) than in the placebo + aspirin arm (2 events). Please provide a break-down summary of these events, by number and type

Studies 011 and 003 were not designed and not powered to evaluate ulcer complications and complications were not included as an efficacy variable in either study. In Study 011, all safety reports were evaluated in order to cover potential upper GI complications. In Study 003, GI complications were defined prospectively (hematemesis, melena, hematochezia, perforation, gastric outlet obstruction and "other"). From the reported data, AZ differentiated GI bleedings by location either in the upper or lower intestine; esomeprazole is only expected to affect upper GI events. Upper GI bleeding was defined as hematemesis and/or melena. Note that hematochezia (rectal red blood) was assessed as a lower GI bleeding, unless it was associated with a significant drop in haemoglobin (Hb), that is, ≥20 g/L. A drop in Hb ≥20 g/L compared to baseline is assessed as a clinically significant event[55],[61].

In Study 011, 6 patients reported AEs of GI bleeding, 4 of which were in the placebo group (1 hemorrhagic gastritis, 1 Mallory-Weiss syndrome with oozing hemorrhage (Hb drop 28 g/L), 1 gastric ulcer hemorrhage and 1 progressive drop in Hb). Three placebo events were reported as SAEs and 1 (hemorrhagic gastritis) as a non-serious AE. All placebo cases, except drop in Hb, were considered to be of upper GI origin. Two cases belonged to the E20 group (1 diverticulitis with Hb drop -31 g/L and 1 rebleeding from a gastric leiomyoma). Of these 2 events, diverticulitis was a lower GI bleeding and the other a rebleeding from a tumor (leiomyoma). None of these 2 events could be expected to be related to acid inhibition (PPI treatment). In summary, in Study 011, 3 events in the placebo group and 1 (neoplasm) in the E20 group were assessed as upper GI bleedings.

In Study 003, the total number of reports assessed as GI complications was 21; 8 were judged as generated in the upper and 13 in the lower GI tract. None of the events were associated with a significant Hb drop. Of the 8 upper GI complications, 1 event was reported in the E40 group (Hb decreased, non-significant). One hematemesis, 1 perforation and 1 dark stool were reported in the E20 mg group. One duodenal bleeding, 2 melena and 1 dark stool were reported in the placebo group. Of the 8 cases with reported upper GI events, 1 was reported as a SAE and 3 as non-serious AEs. Of the 13 lower GI complications, 12 were from patients treated with E20 or E40 and 1 was from a placebo treated patient. Of the 13 cases with a reported lower GI bleeding event none was categorised as a SAE and 5 were reported as non-serious AEs. Of the remaining 8 cases there was 1 hemorrhoid and 7 hematochezia. There were no significant Hb drops reported in any of the 21 cases. Furthermore, none of the patients discontinued study treatment due to the reported lower GI events.

In summary, in Study 003, proportionally more upper GI events were reported in the placebo group. There was a numerical difference in reported lower GI bleed events in favour of placebo. It is AZ's view that this difference is a chance finding and that esomeprazole does not affect lower GI bleed rates. In total, there were a higher numbers of confirmed and potential upper GI complications reported in the placebo groups (7 in 554 exposure years) compared to the esomeprazole groups (5 in 957 exposure years) in Studies 011 and 003. Taken together, the numbers are too small to draw any firm conclusions.

[61] Chan FK, Cryer B, Goldstein JL, Lanas A, Peura DA, Scheiman JM, et al. (2010). A novel composite endpoint to evaluate gastrointestinal (GI) effects of nonsteroidal anti-inflammatory drugs through the entire GI tract. J Rheumatol 2010;37(1):167-74.

Please comment on the formulation design of Axanum versus that of Vimovo; the use of an immediate-release (IR) aspirin component with an enteric-coated esomeprazole component, which is the reverse of what was used with Vimovo, and would like to know if this is an obligatory consequence of the pharmacokinetics of aspirin.

In Vimovo, the esomeprazole component is IR and is designed for twice daily dosing in accordance with the posology for naproxen. The rationale to provide an aspirin/esomeprazole FDC is related to the expected higher compliance to the FDC than to both low-dose aspirin and the PPI component administered individually as separate compounds. The esomeprazole component proposed for registration in Axanum is very similar to that used in the already registered Australian Nexium tablets, formulated as enteric coated pellets. These enteric-coated esomeprazole pellets have a well characterized PK/PD profile that ensures adequate acid suppression following once daily dosing. Hence, both IR aspirin and enteric-coated esomeprazole as monotherapies (and as included in Axanum) are administered once daily, as specified in the individual PIs for CV protection and gastroprotection indications, respectively. The proposed posology for Axanum FDC is therefore the same as for the individual monoproducts. The rationale to use an IR formulation of aspirin is related to the wide use of this formulation and as this is the formulation that can be considered as the "original" one, it therefore can be regarded as the reference product. In addition, "substantial evidence suggests that the influence of enteric coating on bleeding risk is not significant". In the pivotal clinical studies there was a numerical reduction in ulcers with esomeprazole compared to placebo across both subgroups of patients using enteric coated or non-enteric coated aspirin, indicating clinical effectiveness of the proposed formulation of Axanum. Therefore, AZ considered the use of the well characterised formulation of esomeprazole already registered for Nexium appropriate for Axanum. The IR form of aspirin used in Axanum is similar to that characterized in the key PK and PD studies that support this application (Studies 001 and D961FC00011, respectively).

Advisory committee considerations

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy agreed with the Delegate that this product has a negative benefit-risk profile for the proposed indication.

The ACPM was of the view that there is uncertain evidence of clinically appropriate endpoints in the demonstrated reduction in endoscopic ulcers or that the risk of duodenal ulcers was reduced. The pivotal studies were not powered to detect significant reductions in peptic ulcer complications, which are a more clinically relevant end point. The evidence had not established the safety of the combination in patients who require low dose aspirin for reducing the risk of cardiovascular events.

In making this recommendation, the ACPM expressed concern about the evidence and emerging safety signals associated with the reduction of cardiovascular protection and possibly community acquired pneumonia and osteoporotic fractures in patients treated with this fixed dose combination. The ACPM is of the view that this risk is not appropriately balanced with benefit, particularly in view of the intended long term use of this product.

The ACPM noted the unresolved concerns expressed by both ACSOM and in the literature about possible increased rates of cardiovascular and cerebrovascular events in patients on proton-pump inhibitors (PPIs).

The ACPM recommended further studies that take into account the evidence that aspirin causes gastrointestinal erosions in contrast to ulceration and hence investigate the more appropriate clinical end point of prevention of gastrointestinal bleeding in contrast to endoscopic ulcerations.

Outcome

On the 18 April 2012, before a decision had been made by the TGA, the submission was withdrawn by AstraZeneca based on the ongoing, detailed consideration of the likely reimbursement position and subsequent commercial opportunity for Axanum in Australia.

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