Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Axanum 81 mg/20 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains acetylsalicylic acid (aspirin) immediate release and esomeprazole gastro-resistant pellets: 81 mg acetylsalicylic acid (aspirin) and 20 mg esomeprazole (as esomeprazole magnesium trihydrate)

Excipient with known effect: Sucrose (in sugar spheres) max 13.7 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard (capsule)

A two-pieced hard gelatine capsule with reddish pink body and grey cap. Cap is marked E 20 mg and A 81 mg printed in black in radial format.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prevention of thrombotic cardio- and cerebrovascular events in patients requiring continuous low-dose acetylsalicylic acid treatment, and who are in need of prophylaxis against acetylsalicylic acid associated gastric and/or duodenal ulcers.

4.2 Posology and method of administration

The usual dose is 1 capsule once daily. The capsule should be swallowed whole with liquid. It should not be chewed or crushed.

Impaired renal function
Due to the acetylsalicylic acid component, Axanum is contraindicated in patients with severe renal disorder (see section 4.3) and if on concomitant treatment with diuretics, the risk of fluid retention and impaired renal function must be considered.

Impaired hepatic function
Due to the acetylsalicylic acid component, Axanum is contraindicated in patients with cirrhosis of the liver (see section 4.3) and if on concomitant treatment with diuretics, the risk of fluid retention and impaired renal function must be considered.

Elderly (> 65 years)
Dose adjustment is not required in the elderly.

Paediatric population
Axanum should not be used in children younger than 18 years since no data is available.

4.3 Contraindications

Axanum is contraindicated in patients with known hypersensitivity to acetylsalicylic acid, esomeprazole, and

substituted benzimidazoles or any of the excipients.

Because of cross reactions, Axanum is contraindicated in patients who react with symptoms of asthma, rhinitis or urticaria to the administration of acetylsalicylic acid or non-steroidal anti-inflammatory drugs.

Due to the acetylsalicylic acid component, Axanum is also contraindicated in patients with haemophilia, small or large intestinal haemorrhage or other kinds of bleeding such as cerebrovascular haemorrhages, thrombocytopenia, cirrhosis of the liver, severe cardiac insuffiency or severe renal disorder (glomerual filtration rate below 30 ml/min).

Axanum should not be used concomitantly with nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

The need for continuous prevention of thrombotic cardio- and cerebrovascular events should be assessed based on available clinical guidance and national regulatory requirements.

Risk factors for ulcers in patients receiving low dose acetylsalicylic acid include a prior history of peptic ulcer disease (including its complications), concomitant treatment with anticoagulants, corticosteroids and/or NSAIDs, age ≥ 60 years with a history of coronary artery disease or age ≥ 65 years, or the presence of Helicobacter pylori infection.

Axanum is not recommended in cardiovascular emergency situations.

Acetylsalicylic acid
Caution should be observed in patients with bleeding disorders and those treated with anticoagulants. Caution may also be advisable for patients taking SSRIs and/or additional antiplatelets. In patients with mild to moderate cardiac insufficiency, renal disorders or liver disorders, particularly on concomitant treatment with diuretics, the risk of fluid retention and impaired renal function must be considered.

Caution should also be observed in patients with known asthma, hay fever, and chronic airway disease and any other known allergies.

Acetylsalicylic acid decreases the excretion of uric acid when given in low doses. This may cause acute gout in disposed patients (see section 4.5).

It is recommended that patients with a history of gastric and/or duodenal ulcer or ulcer associated complications are tested for Helicobacter pylori before starting low-dose ASA treatment, eradication treatment should be considered if infected.

Axanum should not be used during pregnancy unless the clinical condition of the woman requires treatment with esomeprazole/acetylsalicylic acid (see section 4.6).

Patients should inform physicians and dentists that they are taking Axanum before any surgery is scheduled and before any new medicinal product is taken. Where elective surgery is being considered, the need for Axanum therapy should be reviewed and consideration given whether the medicinal product needs to be temporarily stopped. If patients must temporarily stop antiplatelet therapy, Axanum should be discontinued at least 7 days prior to surgery.

Esomeprazole
In the presence of any alarm symptom (e.g., significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Co-administration of esomeprazole with atazanavir is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in

combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; esomeprazole 20 mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with medicinal products metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. The use of esomeprazole alone with clopidogrel should be discouraged. The use of Axanum with clopidogrel should be considered on an individual patient basis taking account of whether the benefits outweigh the risks (see section 4.5).

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Bone fracture
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10−40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter (see section 5.1).

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Acetylsalicylic acid
Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of acetylsalicylic acid due to its indirect effect on the renin-angiotensin conversion pathway.

Acetazolamide: Concurrent use of acetylsalicylic acid and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.

Anticoagulant Therapy/Inhibitors of platelet aggregation other than acetylsalicylic acid: Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and the effect on platelets. Acetylsalicylic acid can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Combination of anticoagulant therapy and acetylsalicylic acid should be used with caution because of an increased risk of bleeding. There is an increased bleeding risk with combination of acetylsalicylic acid and other antiplatelets.

Anticonvulsants: Salicylate can displace protein-bound phenytoin and valproic acid, leading to decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta Blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of acetylsalicylic acid due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of acetylsalicylic acid due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired. Combination of methotrexate and salicylic acid should be used with caution.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs): The concurrent use of acetylsalicylic acid with NSAIDs may increase the risk of gastric and/or duodenal ulcers and bleeding or lead to decreased renal function.

There are conflicting results from experimental studies where some suggest a decrease in the platelet aggregation inhibiting effect of acetyl salicylic acid with simultaneous administration of ibuprofen. There are no clear results demonstrating a reduction of the cardiovascular effects of acetyl salicylic acid by ibuprofen. The clinical significance of this potential interaction is not established.

The use of corticosteroids may also increase the risk of upper gastric and/or duodenal ulcers and bleeding.

Oral Hypoglycemics: Moderate doses of acetylsalicylic acid may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia.

Uricosuric Agents (Probenecid and Sulfinpyrazone): Salicylates antagonize the uricosuric action of uricosuric agents.

Esomeprazole
Effects of esomeprazole on the pharmacokinetics of other medicinal products
Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal products such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19. For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For saquinavir (with concomitant ritonavir), increased serum levels (80−100%) have been reported during concomitant omeprazole treatment (40 mg qd).

Treatment with omeprazole did not affect the PK of darunavir (with concomitant ritonavir), amprenavir (with concomitant ritonavir), amprenavir (with and without ritonavir), and lopinavir (with concomitant ritonavir).

Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.

Clopidogrel
Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%.

In a study for healthy subjects, there was a decreased exposure by almost 40% of the active metabolite of clopidogrel

when Axanum was given with clopidogrel compared to clopidogrel alone. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in both groups.

Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies.

The use of Axanum with clopidogrel should be considered on an individual patient basis taking these data into account when deciding whether the benefits outweigh the risks.

Medicinal Products metabolised by CYP2C19
Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with medicinal products metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these medicinal products may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on demand therapy. Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn. Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC_{τ} by 15% and 41%, respectively.

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross−over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half−life($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see also section 4.4).

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin, quinidine.

Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.

Unknown mechanism

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.
When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of Axanum may need to be considered.

Effects of other medicinal products on the pharmacokinetics of esomeprazole
Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC_{τ} by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St.John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Axanum in pregnant women.

Axanum should not be used during pregnancy unless the clinical condition of the woman requires treatment with esomeprazole/acetylsalicylic acid.

Acetylsalicylic acid

From the beginning of the sixth month of pregnancy, all prostaglandin synthesis inhibitors may expose:
the foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;
- inhibition of the trombocyte function

the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses
- inhibition of uterine contractions resulting in delayed or prolonged labour.

The anti−aggregating effect and the inhibition of uterine contraction are reversible on withdrawal of treatment.

Intake of acetylsalicylic acid within 5 days of estimated parturition gives an increased tendency to bleeding in the mother and the foetus/newborn. During the last trimester, acetylsalicylic acid should only be given after careful consideration and in low doses. The dose of 150 mg/day should not be exceeded (one tablet per day only). Acetylsalicylic acid should not be administered during the days before expected delivery.

Esomeprazole
For esomeprazole limited clinical data on exposed pregnancies are available. With the racemic mixture, omeprazole, data on a large number of exposed pregnancies indicate no malformative nor foetotoxic effect. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/fetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

Lactation

No studies in lactating women have been performed with the combination of esomeprazole and acetylsalicylic acid.

Acetylsalicylic acid is known to be excreted in limited amounts in human milk.

It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed with esomeprazole.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Axanum therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
There is some evidence that medicinal products which inhibit prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

4.7 Effects on ability to drive and use machines

Axanum is not likely to affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The clinical programme in patients were conducted with the free combination of low-dose ASA and esomeprazole, with low-dose ASA doses ranging from 75 to 325 mg, according to physician's prescription. No new safety findings were identified during free combination treatment in the overall study population (n=2100) compared to the well-established safety profiles of the individual active substances acetylsalicylic acid and esomeprazole.

The most commonly reported adverse drug reactions during treatment with the free combination of low-dose ASA and esomeprazole were diarrhoea, headache, abdominal pain, constipation, dyspepsia, flatulence and nausea/vomiting. In most cases, the events resolved during continued treatment.

Tabulated summary of adverse reactions
Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are defined according to the following convention:

Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from available data)

Axanum
The following adverse adverse drug reactions have been reported in patients taking the free combination of low-dose ASA (75−325 mg/day) and esomeprazole (20−40 mg/day) during clinical trials.

	Common	**Uncommon**	**Rare**
Blood and lymphatic system disorders			thrombocytopenia
Immune system disorders		Allergic reaction	hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders		peripheral oedema, gout, hypoglycaemia	hyponatraemia
Psychiatric disorders		insomnia	depression
Nervous system disorders	headache	dizziness, paraesthesia, somnolence	taste disturbance
Ear and labyrinth disorders		vertigo	tinnitus
Respiratory, thoracic and mediastinal disorders		rhinitis, asthma, epistaxis	bronchospasm
Gastrointestinal disorders	abdominal pain, diarrhoea, dyspepsia, flatulence, nausea/vomiting, constipation	dry mouth	gastric ulcer, duodenal ulcer, stomatitis, gastrointestinal candidiasis
Hepatobiliary disorders		increased liver enzymes	hepatitis with or without jaundice

Skin and subcutaneous tissue disorders		dermatitis, pruritus, urticaria, rash	alopecia
Musculoskeletal and connective tissue disorders			arthralgia, myalgia
General disorders and administration site disorders			malaise

Acetylsalicylic acid
In addition the following adverse drug reactions have been reported in patients taking acetylsalicylic acid during clinical trials and through postmarketing reports.

Blood and lymphatic system disorders
Rare: Microcytic anaemia

Psychiatric disorders
Very rare: Confusion

Gastrointestinal disorders
Rare: Gingival bleeding, severe gastrointestinal bleeding

Investigations
Common: Increased bleeding time

Renal and urinary disorders
Rare: Kidney function disturbances

Skin and subcutaneous tissue disorders
Very rare: Erythema multiforme

Vascular disorders
Uncommon: Spontaneous bleeding, severe bleeding reactions

Esomeprazole:
In addition the following adverse drug reactions have been identified or suspected in the clinical trials programme for enteric-coated esomeprazole and/or from post-marketing use. None were found to be dose-related.

Blood and lymphatic system disorders
Rare: Leukopenia
Very rare: Agranulocytosis, pancytopenia

Metabolism and nutrition disorders
Not known: Hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia

Psychiatric disorders
Rare: Agitation, confusion
Very rare: Aggression, hallucinations

Eye disorders
Rare: Blurred vision

Gastrointestinal disorders
Not Known: Microscopic colitis

Hepatobiliary disorders
Very rare: Hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders
Rare: Photosensitivity
Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal and connective tissue disorders
Uncommon: Fracture of the hip, wrist or spine
Very rare: Muscular weakness

Renal and urinary disorders
Very rare: Interstitial nephritis

Reproductive system and breast disorders
Very rare: Gynaecomastia

General disorders and administration site disorders
Rare: Hyperhidrosis

4.9 Overdose

Acetylsalicylic acid
Overdose of acetylsalicylic acid may result in the following symptoms and signs, which may appear after some hours:

- Dizziness, tinnitus, impaired hearing, irritation, anxiety, hallucinations, tremor, asterixis, hyperventilation, thirst, rash, sweating, nausea, vomiting, abdominal pain.
- In severe cases unconsciousness convulsions, coma, hyperthermia.
- Initially respiratory alkalosis in adults.
- Metabolic acidosis in children and after large doses in both adults and children.
- Hyperglycaemia or hypoglycaemia (in children).
- Dehydration, potassium deficiency, oliguri, hemorrhagic pnenomena, impaired liver function, pancreatitis, pulmonary edema, rhabdomyolysis, renal insufficiency.

In case of overdose the following actions should be applied:

- Induction of vomiting or gastric lavage.
- Repeated administration of activated charcoal.
- Laxative.
- Rehydration, correction of metabolic alkalosis and electrolyte imbalance.
- Bicarbonate solution should be infused intravenously, if possible in sufficient quantity to maintain alkaline diuresis to increase elimination of the medicinal product.
- Glucose should be administered to control the metabolic acidosis.
- Coagulation status should be followed and it may be necessary to give blood transfusion or thrombocyte concentrate and fresh plasma, and vitamin K.
- Hemodialysis should be performed in severe cases and in patients with renal impairment.
- Symptomatic treatment of hyperthermia, pulmonary and brain edema.

Esomeprazole
The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Platelet aggregation inhibitors excl. heparin: ATC code: B01AC56.

Acetylsalicylic acid
Acetylsalicylic acid inhibits the formation of the eicosanoid thromboxane A2 by covalent, irreversible, acetylation of a serine near the active site of cyclooxygenase, the enzyme producing the cyclic endoperoxide precursor of thromboxane A2.

Thromboxane A2 is a short-lived inducer of platelet aggregation and a potent vasoconstrictor.

Platelets can not synthesise new enzyme so the effects persists throughout the entire life span of the thrombocyte which is 7−10 days.

The prophylactic and therapeutic effect of acetylsalicylic acid in arterial thromboembolism is dependent on this effect. The dose needed to inhibit platelet aggregation is considerably lower than the analgesic or anti-inflammatory dose level. To obtain a continuous inhibition of thromboxane A2 synthesis a daily dose of 75 mg acetylsalicylic acid is appropriate.

Acetylsalicylic acid inhibits renal prostaglandin synthesis. This effect is insignificant in patients with normal renal function. In patients with chronic renal insufficiency, cardiac insufficiency or liver insufficiency as well as conditions characterised by changing plasma volumes, the inhibited synthesis of prostaglandins may cause acute renal insufficiency, fluid retention and cardiac insufficiency.

Esomeprazole
Esomeprazole is the *S*-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

Site and mechanism of action
Esomeprazole is a weak base and 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 and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion
After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for 5 days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6−7 hours after dosing on day 5.

After 5 days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GERD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for esomeprazole 20 mg 76%, 54% and 24%. Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

Therapeutic effects of acid inhibition
Coadministration of esomeprazole 20 or 40 mg with low dose acetylsalicylic acid (75−325 mg) was significantly better than placebo in prevention of gastric and/or duodenal ulcers associated with low-dose acetylsalicylic acid therapy in patients at risk (prior history of ulcer disease, age ≥ 60 years with a history of coronary artery disease or age ≥65 years).

Other effects related to acid inhibition

During treatment with antisecretory medicinal products serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Literature reports indicate that proton pump inhibitor treatment should be stopped at least 5 days before CgA measurement. If CgA and gastrine levels have not normalised after 5 days, measurements should be repeated 14 days after cessation of esomeprazole treatment.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole. The findings are considered to be of no clinical significance.

During long-term treatment with antisecretory medicinal products gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly also *Clostridium difficile* in hospitalized patients.

5.2 Pharmacokinetic properties

Absorption and distribution
Acetylsalicylic acid
Acetylsalicylic acid is mainly absorbed from upper small intestine but also from the stomach. Maximal plasma concentration is reached within 40 minutes. Acetylsalicylic acid is hydrolysed with a half-life of 30 minutes to salicylic acid. Hydrolysis of acetylsalicylic acid takes place in plasma, liver and erythrocytes. The half-life of salicylic acid is dose dependent but generally 2−3 hours at doses below 3 g. At therapeutic doses salicylic acid is to 80% bound to albumin. Salicylic acid and its metabolites are excreted in the urine.

Esomeprazole
Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the R-isomer is negligible. Maximum plasma concentration of esomeprazole occurs approximately 3 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68%, respectively. The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 l/kg body weight. Esomeprazole is 97% plasma protein bound. Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Metabolism and Excretion
Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time - and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is

found in urine.

Special patient populations
Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%.

These findings have no implications for the posology of Axanum.

The metabolism of esomeprazole is not significantly changed in elderly subjects (71−80 years of age).
Following a single dose of 40 mg esomeprazole the mean area under the plasma concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the posology of Axanum.

The metabolism of esomeprazole in patients with mild to moderate liver impairment may be impaired. The metabolic rate is decreased in patients with severe liver impairment resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe hepatic impairment. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

5.3 Preclinical safety data

Acetylsalicylic acid
Acetylsalicylic Acid: Single-dose studies have shown that the oral toxicity of ASA is low. Repeat-dose toxicity studies have shown that levels up to 200 mg/kg/day are well tolerated in rats; dogs appear to be more sensitive, probably due to the high sensitivity of canines to the ulcerogenic effects of NSAIDs. No genotoxicity or clastogenicity issues of concern have been found with ASA. Although no formal carcinogenicity studies have been performed with ASA, it has been shown that it is not a tumour promoter. Reproduction toxicity data show that ASA is teratogenic in several laboratory animals. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Esomeprazole
Preclinical bridging studies reveal no particular hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction. Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

Esomeprazole and acetylsalicylic acid
Three months' oral administration of a combination of esomeprazole and acetylsalicylic acid in a repeat-dose toxicity study in dogs only resulted in additive effects. No new or unexpected toxicological findings were seen in this study.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Esomeprazole component
glycerol monostearate 40−55
hydroxypropylcellulose
hypromellose
magnesium stearate
methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30 per cent (may contain sodium dodecyl sulphate and polysorbate 80)
polysorbate 80
sodium stearyl fumarate
sugar spheres (contain sucrose and maize starch)
talc
triethyl citrate

Acetylsalicylic acid component
low-substituted hydroxypropylcellulose

Hard gelatine capsule, reddish pink/grey size 3
gelatine
iron oxide red (E172)
iron oxide black (E172)
titanium dioxide (E171)

Ink black, SW-9008
iron oxide black (E172)
potassium hydroxide
shellac
propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

Bottle:
Keep the bottle tightly closed in order to protect from moisture.

Blister:
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/aluminium perforated blister pack of 10 capsules per blister
Pack sizes of 10, 30 and 90 capsules in perforated blister
Pack sizes of 30x1 and 90x1 capsules in perforated unit dose blister

HDPE bottle containing silica-gel desiccant with a child-resistant, induction sealed polypropylene closure. The sachet containing the desiccant is not meant to be consumed. Pack-sizes of 30 and 90 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited
600 Capability Green
Luton LU1 3LU
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 970/063/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 31st August 2012

10 DATE OF REVISION OF THE TEXT

May 2013