PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ENTELROMESIS 75/75 mg, film coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains clopidogrel hydrogen sulphate equivalent to clopidogrel base 75 mg, and acetylsalicylic acid (ASA) (aspirin) 75 mg.

Each tablet contains mannitol 64 mg and sugar (lactose monohydrate 2,80 mg)

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet.

Yellow coloured, oval shaped, film coated tablets debossed with “I” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENTELROMESIS is indicated for the reduction of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA).

ENTELROMESIS is a fixed-dose combination product for continuation of therapy in:

PROFESSIONAL INFORMATION

Acute Coronary Syndrome:

For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave myocardial infarction [MI]) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG (coronary artery bypass graft), clopidogrel in combination with ASA has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischaemia.

For patients with ST-segment elevation acute myocardial infarction, clopidogrel in combination with ASA has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke.

4.2 Posology and method of administration

Acute Coronary Syndrome:

ENTELROMESIS should be given as a single daily dose (i.e. one tablet daily). ENTELROMESIS is used following an initial loading dose of clopidogrel in combination with ASA.

In patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, but the maximum benefit was seen at 3 months.

In patients with ST segment elevation acute myocardial infarction: Therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting. For patients older than 75 years of age therapy should be initiated without a loading dose of clopidogrel.

Special populations

Pharmacogenetics:

CYP2C19 poor metaboliser status is associated with diminished antiplatelet response to clopidogrel. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Paediatric population

ENTELROMESIS is not indicated for use in children under the age of 18 years as safety and efficacy have not been established.

Method of administration

For oral use.

ENTELROMESIS may be given with or without food.

Missed dose:

Medical practitioners should advise patients who forget to take ENTELROMESIS to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

Due to the presence of clopidogrel and acetylsalicylic acid (aspirin) in the medicine, ENTELROMESIS is contraindicated in case of:

- hypersensitivity to clopidogrel, acetylsalicylic acid or to any of the ingredients of ENTELROMESIS (see section 6.1)
- active or history of pathological bleeding such as recurrent peptic ulcer/haemorrhage/perforations or intracranial haemorrhage
- safety and efficacy in children below the age of 18 have not been established. ASA has been implicated in Reye's syndrome, a rare but serious illness in children and teenagers with chickenpox and influenza. A medical practitioner should be consulted before aspirin is used in these patients
- safety and efficacy in pregnancy and lactation have not been established (see section 4.6)
- severe hepatic impairment
- thrombocytopenia and platelet dysfunction.

In addition, due to the presence of ASA, ENTELROMESIS is also contraindicated in:

- patients with hypersensitivity (allergy) to non-steroidal anti-inflammatory drugs (NSAIDs) and syndrome of asthma, rhinitis, and nasal polyps. Patients with pre-

existing mastocytosis, in whom the use of acetylsalicylic acid may induce severe hypersensitivity reactions (including circulatory shock with flushing, hypotension, tachycardia and vomiting)

- patients with severe renal impairment
- patients with heart failure
- patients with a history of gastrointestinal bleeding, ulceration or perforation (PUBs) related to previous NSAIDs
- pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) HAS BEEN REPORTED TO OCCUR WITH ENTELROMESIS DURING POST-MARKETING EXPERIENCE. MOST CASES WERE REPORTED IN THE FIRST TWO WEEKS OF TREATMENT. PRESCRIBERS SHOULD ALSO WARN PATIENTS ABOUT THE SIGNS AND SYMPTOMS OF THROMBOTIC THROMBOCYTOPENIC PURPURA. IT IS CHARACTERISED BY THROMBOCYTOPENIA AND MICROANGIOPATHIC HAEMOLYTIC ANAEMIA ASSOCIATED WITH EITHER NEUROLOGICAL FINDINGS, RENAL DYSFUNCTION OR FEVER. TTP IS A POTENTIALLY FATAL CONDITION REQUIRING PROMPT TREATMENT, INCLUDING PLASMAPHERESIS (PLASMA EXCHANGE).

Recent transient ischaemic attack or stroke

In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of aspirin and clopidogrel has been shown to increase major bleeding.

Acquired haemophilia

Following use of clopidogrel, acquired haemophilia has been reported. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and ENTELROMESIS should be discontinued.

Fluid retention and oedema

In view of the inherent potential of NSAIDs, including ASA, to cause fluid retention, heart failure may be precipitated in some compromised patients. As fluid retention and oedema have been reported in association with ENTELROMESIS therapy, caution is required in patients with a history of hypertension and/or heart failure.

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding, ulceration and perforation (PUBs) which may be fatal.

Due to the presence of ASA caution is required in the following:

- patients with a history of asthma or allergic disorders since they are at increased risk of hypersensitivity reactions
- patients with gout since low doses of ASA increase serum uric acid concentrations
- children: as there is an association between ASA and Reye's syndrome (a very

rare disease which can be fatal) when ASA is given to children

- alcohol may increase the risk of gastrointestinal injury when taken with ASA. Alcohol should therefore be used with caution in patients taking ENTELROMESIS (see section 4.5). Patients should be counselled about the bleeding risks involved with chronic, heavy alcohol use while taking ENTELROMESIS
- in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, ENTELROMESIS must be administered under close medical supervision due to the risk of haemolysis (see section 4.8)
- concomitant treatment with levothyroxine and salicylates, specifically at doses greater than 2,0 g/day, should be avoided (see section 4.5).

Bleeding and haematological disorders

ENTELROMESIS produces irreversible inhibition of platelet aggregation for the life of the platelet, which is 7-10 days.

Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever such suspected clinical symptoms arise during the course of treatment (see section 4.8). As there is a risk of bleeding intensity, concomitant administration of ENTELROMESIS with warfarin is not recommended (see section 4.5).

Caution is required when administering ENTELROMESIS to patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions associated with bleeding diathesis as well as in patients receiving treatment with other non-steroidal anti-inflammatory medicines including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa

inhibitors, selective serotonin reuptake inhibitors (SSRIs), or CYP2C19 strong inducers, or thrombolytics (see section 4.5). Patients should be monitored continuously and carefully for any signs of bleeding (including occult bleeding) especially but not limited to during the first weeks of treatment and/or after invasive cardiac procedures or surgery.

ENTELROMESIS should be discontinued 7 days prior to surgery in those patients who are to undergo elective surgery where an antiplatelet effect is not desired.

The concomitant administration of ENTELROMESIS with oral anticoagulants is not recommended since it may increase the intensity of bleeding (see section 4.5).

ENTELROMESIS prolongs bleeding time and should therefore be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intra-ocular).

Spinal and epidural anaesthesia should not be administered to a patient taking ENTELROMESIS or for 7 days thereafter. No lumbar puncture should be done during these 7 days due to risk of haematoma formation following lumbar puncture or spinal and epidural anaesthesia.

Patients should be told that it may take longer than usual to stop bleeding whilst on ENTELROMESIS therapy, and that they should report any unusual bleeding (site or duration) to their medical practitioner.

Patients should inform medical practitioners and dentists that they are taking ENTELROMESIS before any surgery is scheduled and before any new medicine is taken.

Gastrointestinal

In patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia), peptic ulcer, gastroduodenal haemorrhage or minor upper gastrointestinal symptoms, ENTELROMESIS should be used with caution as the condition may be exacerbated or may be due to gastric ulceration which in turn may lead to gastric bleeding.

In patients with a history of ulcers, and the elderly the risk of gastrointestinal bleeding, ulceration or perforation (PUBs) is higher with increasing doses of ENTELROMESIS. Should gastrointestinal bleeding, perforation or ulceration occur in patients receiving ENTELROMESIS, therapy should be stopped.
Gastrointestinal side effects including stomach pain, heartburn, nausea, vomiting, and GI bleeding may occur. Although minor upper GI symptoms (such as dyspepsia) are common and can occur anytime during therapy, medical practitioners should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Patients should be told about signs and symptoms of GI side effects and what steps to take if they occur.

In patients concomitantly receiving nicorandil and NSAIDs including acetylsalicylic acid (ASA) and lysine acetylsalicylate (LAS), there is an increased risk for severe

complications such as gastrointestinal ulceration, perforation and haemorrhage (see section 4.5).

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported.
ENTELROMESIS should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cytochrome P450 2C19 (CYP2C19)

Pharmacogenetics:

In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Poor metabolisers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses may exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function.
Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy (see section 5.2: Pharmacogenetics and section 4.2).
Use of medicines that induce the activity of CYP2C19 would be expected to result in increased medicine levels of the active metabolite of clopidogrel and might potentiate the bleeding risk. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged (see section 4.5).

CYP2C8 substrates

Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products (see section 4.5).

Cross-reactivity among thienopyridines

As cross-reactivity among thienopyridines has been reported, patients should be evaluated for history of hypersensitivity to another thienopyridine (such as ticlopidine, prasugrel) (see section 4.8).

Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological reactions such as thrombocytopenia and neutropenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for cross-reactivity is advised.

Hepatic impairment

ENTELROMESIS is contraindicated in patients with severe hepatic impairment (see section 4.3).

Caution is advised in patients with mild and moderate hepatic impairment.

Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Therefore ENTELROMESIS should be used with caution in this population.

Renal impairment

ENTELROMESIS is contraindicated in patients with severe renal impairment (see section 4.3).

Therapeutic experience with ENTELROMESIS is limited in patients with mild to moderate renal impairment.

ENTELROMESIS should therefore be used with caution in this population.

Excipients with known effect:

ENTELROMESIS contains lactose. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ENTELROMESIS.

ENTELROMESIS contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicines and other forms of interaction

There are no studies on the concomitant use of clopidogrel and acetylsalicylic acid with other medicines. The information below was obtained with clopidogrel or ASA alone. Safety of ENTELROMESIS and the concomitant use with the medicines mentioned below have not been established.

Medicines associated with bleeding risk

There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicines associated with bleeding risk should be undertaken with caution (see section 4.4).

Nicorandil

In patients concomitantly receiving nicorandil and NSAIDs including acetylsalicylic acid (ASA) and lysine acetylsalicylate (LAS), there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage (see section 4.4).

Injectable anticoagulants

In healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel, however, as a pharmacodynamic interaction between ENTELROMESIS and heparin is possible, concomitant use should be undertaken with caution.

Thrombolytics

The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction with the incidence of clinically significant bleeding being similar to that as observed when thrombolytic medicines and heparins are co-administered with acetylsalicylic acid. However, the concomitant use of ENTELROMESIS with thrombolytic medicines should be undertaken with caution.

Oral anticoagulants

Concomitant administration of warfarin with ENTELROMESIS is not recommended due to the increased risk of bleeding (see section 4.4).

Glycoprotein IIb/IIIa inhibitors

ENTELROMESIS should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and who receive concomitant glycoprotein IIb/IIIa inhibitors.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

In healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. Consequently, the concomitant use of NSAIDs, including Cox-2 inhibitors, is not recommended with ENTELROMESIS (see section 4.4).

When they are dosed concomitantly, experimental data suggests that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation (see section 5.1). However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Selective Serotonin Reuptake Inhibitors (SSRIs)

The concomitant administration of SSRIs with clopidogrel should be undertaken with caution as SSRIs affect platelet activation and increase the risk of bleeding.

Other concomitant therapy with clopidogrel:

Inducers of CYP2C19

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicines that induce the activity of this enzyme would be expected to result in increased medicine levels of the active metabolite of clopidogrel.

Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged (see section 4.4).

Inhibitors of CYP2C19

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicine that inhibit the activity of this enzyme would be expected to result in reduced medicine levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g., omeprazole and esomeprazole) should be discouraged (see section 4.4 and section 5.2, Pharmacogenetics). If a proton pump inhibitor is to be used concomitantly with ENTELROMESIS, consider using one with less CYP2C19 inhibitory activity.

Other medicinal products

No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital or estrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

Data from studies with human liver microsomes indicated that clopidogrel could inhibit the activity of one of the Cytochrome P450 (CYP) enzymes (CYP2C9). This could potentially lead to increased plasma levels of medicines such as phenytoin, tolbutamide, torsemide, tamoxifen, fluvastatin and NSAIDs which are metabolised by CYP2C9. Data indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

CYP2C8 substrate medicines

Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. *In vitro* studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and medicines primarily cleared by CYP2C8 metabolism (e.g. repaglinide, paclitaxel) should be undertaken with caution.

Rosuvastatin

Clopidogrel has been shown to increase rosuvastatin exposure in patients by 1.4-fold (AUC) without effect on C_{max}, after repeated administration of a 75 mg clopidogrel dose.

Other concomitant therapy with ASA

Interactions with the following medicinal products have been reported with ASA:

Uricosurics

Caution is required because ASA may inhibit the effect of uricosuric agents through competitive elimination of uric acid.

Methotrexate

Due to the presence of ASA, methotrexate used at doses higher than 20 mg/week should be used with caution with ENTELROMESIS as it can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity.

Metamizole

Metamizole may reduce the effect of ASA on platelet aggregation when taken concomitantly. Therefore, this combination should be used with caution in patients taking low-dose ASA for cardio-protection.

NSAIDs

Use of two or more NSAIDs concomitantly could result in an increase in side effects.

Corticosteroids

Increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

Selective serotonin reuptake inhibitors (SSRIs)

Increased risk of gastrointestinal bleeding.

Acetazolamide

Due to the increased risk of metabolic acidosis, caution is recommended when co-administering salicylates with acetazolamide.

Varicella vaccine

Cases of Reye's syndrome have occurred following the use of salicylates during varicella infections. It is therefore recommended that patients not be given salicylates for an interval of six weeks after receiving the varicella vaccine. (see section 4.4).

Levothyroxine

Thyroid hormone levels should be monitored as salicylates, specifically at doses greater than 2,0 g/day, may inhibit binding of thyroid hormones to carrier proteins and thereby lead to an initial transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels.

Valproic acid

The concomitant administration of salicylates and valproic acid may result in decreased valproic acid protein binding and inhibition of valproic acid metabolism resulting in increased serum levels of total and free valproic acid.

Tenofovir

Concomitant administration of tenofovir disoproxil fumarate and NSAIDs may increase the risk of renal failure.

Other interactions with ASA

Interactions with the following medicinal products with higher (anti-inflammatory) doses of ASA have also been reported: angiotensin converting enzyme (ACE) inhibitors, acetazolamide, anticonvulsants (phenytoin and valproic acid), beta blockers, diuretics, and oral hypoglycaemic medicines.

Alcohol

Alcohol, when taken with ASA, may increase the risk of gastrointestinal injury. Therefore, alcohol should be used with caution in patients taking ENTELROMESIS (see section 4.4).

Other interactions with clopidogrel and ASA

More than 30 000 patients who entered into clinical trials with clopidogrel plus ASA, at maintenance doses lower than or equal to 325 mg received a variety of concomitant medications including diuretics, beta blockers, ACE Inhibitors, calcium antagonists, cholesterol lowering medicines, coronary vasodilators, antidiabetic medicines (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

Apart from the specific medicine interaction information described above, interaction studies with ENTELROMESIS and some medicines commonly administered in patients with atherothrombotic disease have not been performed.

Opioid agonists

Co-administration of opioid agonists has the potential to delay and reduce the absorption of an oral P2Y12 inhibitor such as clopidogrel, presumably because of slowed gastric emptying. The clinical relevance is unknown. Consider the use of a parenteral antiplatelet medicines in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

4.6 Fertility, pregnancy and lactation

Pregnancy

ENTELROMESIS is contraindicated during pregnancy (see section 4.3).

Breastfeeding

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether clopidogrel is excreted in human breast milk. ASA is known to be excreted in human breast milk.

ENTELROMESIS is contraindicated whilst breastfeeding (see section 4.3).

Fertility

There are no fertility data with clopidogrel/acetylsalicylic acid.

4.7 Effects on ability to drive and use machines

ENTELROMESIS has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Bleeding is the most common reaction reported both in clinical studies where frequencies varied from common to very common, as well as in post-marketing experience.

Tabulated summary of adverse reactions ENTELROMESIS

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent Frequency unknown	Thrombocytopenia (sometimes severe), increased bleeding time, leucopenia, eosinophilia, neutropenia (sometimes severe), platelets decreased, aplastic anaemia Bleeding*
Nervous system disorders	Less frequent	Intracranial bleeding, headache, dizziness, paraesthesia

Eye disorders	Less frequent	Eye bleeding (mainly conjunctival), ocular, retinal
Ear and labyrinth disorders	Less frequent	Vertigo
Vascular disorders	Frequent	Haematoma
Respiratory, thoracic and mediastinal disorders	Frequent	Epistaxis
Gastrointestinal disorders	Frequent Less frequent	Dyspepsia, abdominal pain, diarrhoea, gastrointestinal haemorrhage Nausea, gastritis, flatulence, constipation, vomiting, gastric ulcer, duodenal ulcer
Skin and subcutaneous tissue disorders	Frequent Less frequent	Bruising Rash, pruritus, purpura
Renal and urinary disorders	Less frequent	Haematuria
General disorders and administrative site conditions	Frequent	Bleeding at the puncture site

*Post marketing events.

Tabulated summary of adverse reactions Clopidogrel

System Organ Class	**Frequency**	**Side effects**

Blood and lymphatic system disorders	Frequency unknown	Serious cases of bleeding, mainly skin, musculoskeletal (haemarthrosis), eye (conjunctival, ocular, retinal) and respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), epistaxis, haematuria and haemorrhage of operative wound; cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal haemorrhage), acquired haemophilia A, serious haemorrhage in patients taking ENTELROMESIS with or without heparin, thrombotic thrombocytopenic purpura (TTP), aplastic anaemia/pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia
Immune system disorders	Frequency unknown	Anaphylactoid reactions, serum sickness, cross-reactive medicine hypersensitivity among thienopyridines, such as ticlopidine or prasugrel, insulin autoimmune syndrome, which can lead to severe hypoglycaemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)
Cardiac disorders	Frequency unknown	Kounis syndrome (vasospastic allergic angina/allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel
Psychiatric disorders	Frequency unknown	Confusion, hallucinations
Nervous system disorders	Frequency unknown	Taste disturbances, ageusia
Vascular disorders	Frequency unknown	Vasculitis, hypotension

Respiratory, thoracic and mediastinal disorders	Frequency unknown	Bronchospasm, interstitial pneumonitis, eosinophilic pneumonia
Gastrointestinal disorders	Frequency unknown	Colitis (including ulcerative or lymphocytic colitis), stomatitis, pancreatitis
Hepatobiliary disorders	Frequency unknown	Acute liver failure, hepatitis, abnormal liver function test
Skin and subcutaneous tissue disorders	Frequency unknown	Maculopapular, erythematous or exfoliative rash; urticaria; pruritus; angioedema; bullous dermatitis (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP)); drug-induced hypersensitivity syndrome (DiHS), drug rash with eosinophilia and systemic symptoms (DRESS), eczema; lichen planus
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Arthritis, arthralgia, myalgia
Renal and urinary disorders	Frequency unknown	Glomerulonephritis, increased blood creatinine
Reproductive system and breast disorders	Frequency unknown	Gynaecomastia
General disorders and administrative site conditions	Frequency unknown	Fever

Tabulated summary of adverse reactions ASA

System Organ Class	**Frequency**	**Side effects**

Blood and lymphatic system disorders	Frequency unknown	Thrombocytopenia, haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, pancytopenia, bicytopenia, aplastic anaemia, bone marrow failure, agranulocytosis, neutropenia, leukopenia
Immune system disorders	Frequency unknown	Anaphylactic shock, aggravation of allergic symptoms of food allergy
Cardiac disorders	Frequency unknown	Kounis syndrome in the context of a hypersensitivity reaction due to ASA
Metabolism and nutrition disorders	Frequency unknown	Hypoglycaemia, gout
Nervous system disorders	Frequency unknown	Intracranial haemorrhage (may be fatal, especially in the elderly)
Ear and labyrinth disorders	Frequency unknown	Hearing loss or tinnitus
Vascular disorders	Frequency unknown	Hypertension, cardiac failure, vasculitis including Henoch-Schönlein purpura
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Non-cardiogenic pulmonary oedema with chronic use and in the context of a hypersensitivity reaction due to ASA

Gastrointestinal disorders	Frequent	Gastro-duodenal ulcer/perforations, upper gastrointestinal symptoms such as gastralgia, peptic ulcers, small (jejunum and ileum) and large (colon and rectum) intestinal ulcers, perforation or gastrointestinal bleeding, sometimes fatal, oesophagitis, oesophageal ulceration, perforation, erosive gastritis, erosive duodenitis, colitis, (these reactions may or may not be associated with haemorrhage, and may occur at any dose of ASA and in patients with or without warning symptoms or a previous history of serious gastrointestinal events), nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis,
		acute pancreatitis in the context of a hypersensitivity reaction due to ASA
Hepatobiliary disorders	Frequency unknown	Elevation of hepatic enzymes, liver injury, mainly hepatocellular, chronic hepatitis
Skin and subcutaneous tissue disorders	Frequency unknown	Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis; fixed eruption
Renal and urinary disorders	Frequency unknown	Renal failure, acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics)
General disorders and administrative site conditions	Frequency unknown	Oedema

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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An email can be sent directly to the company,

pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

There is no information concerning overdosage with ENTELROMESIS - the fixed-dose combination tablets, however due to the pharmacological activity of both clopidogrel and ASA individually, overdose may be associated with increased bleeding and subsequent bleeding complications.

Symptoms of the individual active ingredients are as follows:

Clopidogrel:

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications.

Acetylsalicylic acid (ASA):

Moderate overdose: dizziness, ringing in the ears, sensation of reduced hearing, headaches, vertigo and gastrointestinal symptoms (nausea, vomiting and gastric pain).

Severe overdose: fever, hyperventilation, ketosis, respiratory alkalosis, metabolic acidosis, coma, cardiovascular collapse, respiratory failure, severe hypoglycaemia, hyperthermia and perspiration, leading to dehydration.

Non-cardiogenic pulmonary oedema can occur with acute and chronic acetylsalicylic acid overdose (see section 4.8).

Management of overdose:

Clopidogrel:

Appropriate therapy should be considered if bleedings are observed. No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

Further treatment is symptomatic and supportive.

Acetylsalicylic acid (ASA):

If a toxic dose has been ingested, admission to hospital is necessary. With moderate intoxication an attempt can be made to induce vomiting;. Activated charcoal (adsorbent) and sodium sulphate (laxative) are then administered. Alkalising of the urine (250 mmol sodium bicarbonate for 3 hours) while monitoring the urine pH is indicated.

Haemodialysis is the preferred treatment for severe intoxication. Treat other signs of intoxication symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PROFESSIONAL INFORMATION

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excl. Heparin.

ATC code: B01AC30.

Pharmacological classification: A 8.2 Anticoagulants

Mechanism of action

Clopidogrel:

Clopidogrel is a specific and potent inhibitor of platelet aggregation.

Clopidogrel is a promedicine, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation.

The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP- mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of the lifespan (approximately 7 - 10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicines, not all patients will have adequate platelet inhibition.

Dose-dependent inhibition of platelet aggregation was noted 2 hours after single oral doses of clopidogrel.

Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40 % and 60 %. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

Acetylsalicylic acid (ASA):

Acetylsalicylic acid inhibits platelet aggregation by irreversible inhibition of prostaglandin cyclo-oxygenase and thus inhibits the generation of thromboxane A2, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

5.2 Pharmacokinetic properties

Clopidogrel:

Absorption:

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2,2 - 2,5 ng/ml after a single 75 mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50 %, based on urinary excretion of clopidogrel metabolites.

Distribution:

Clopidogrel and the main circulating (inactive) metabolite bind reversibly *in vitro* to human plasma proteins (98 % and 94 % respectively). The binding is non-saturable *in vitro* over a wide concentration range.

Biotransformation:

Clopidogrel is extensively metabolised by the liver. *In vitro* and *in vivo*, clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85 % of circulating metabolites), and one mediated by multiple cytochromes P450.

Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

Elimination:

Following an oral dose of ^{14}C-labelled clopidogrel in man, approximately 50 % was excreted in the urine and approximately 46 % in the faeces in the 120-hour interval after dosing. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

Pharmacogenetics

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and

antiplatelet effects, as measured by *ex vivo* aggregation assays, differ according to CYP2C19 genotype. The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are non-functional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in white (85 %) and Asian (99 %) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to, CYP2C19*4, *5, *6, *7, and *8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metaboliser genotypes are approximately 2 % for whites, 4 % for blacks and 14 % for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultra-rapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63 - 71 % compared to extensive metabolisers. At steady state, platelet aggregation inhibition (5 µM ADP) was decreased in poor metabolisers with mean IPA of 37 % compared to 58 % in the extensive metabolisers and 60 % in the intermediate metabolisers. An appropriate dose regimen for this patient population has not been established in clinical outcome trials. In a meta-analysis including 6 studies of 335 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28 % for intermediate metabolisers, and 72 % for poor metabolisers while platelet aggregation inhibition (5 µM ADP) was decreased with differences in IPA of 5,9 % and 21,4 %, respectively, when compared to extensive metabolisers.

There is some evidence that patients who are either intermediate or poor metabolisers may have a higher rate of cardiovascular events (death, myocardial infarction, stroke or stent thrombosis) compared to extensive metabolisers.

Pharmacokinetics in special patient groups

The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations.

Elderly

In elderly (≥ 75 years) volunteers compared to young healthy volunteers, there were no differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renal impairment

After repeated administration of 75 mg clopidogrel/day in subjects with severe renal impairment (creatinine clearance from 5 to 15 ml/min) ADP-induced platelet aggregation was lower (25 %) than that observed in healthy subjects, however, the prolongation of bleeding was similar to that seen in healthy subjects receiving 75 mg clopidogrel per day.

Ethnicity

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to ethnicity (see section 5.2, Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

Acetylsalicylic acid (ASA):

Absorption:

Following absorption, the ASA in the fixed dose combination tablet is hydrolised to salicylic acid with peak plasma levels of salicylic acid occurring within 1 hour of dosing, such that plasma levels of ASA are essentially undetectable 1,5 - 3 hours after dosing.

Distribution:

ASA is poorly bound to plasma proteins and its apparent volume of distribution is low (10 l). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration dependent (nonlinear). At low concentrations (< 100 µg/ml), approximately 90 % of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and foetal tissues.

Biotransformation and Elimination:

The ASA in the fixed dose combination tablet is rapidly hydrolised in plasma to salicylic acid, with a half-life of 0,3 - 0,4 hours for ASA doses from 75 to 100 mg. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid in the fixed dose combination tablet has a plasma half-life of approximately 2 hours.

Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10 - 20 g), the plasma half-life may be increased to over 20 hours. At high ASA doses, the elimination of salicylic acid follows zero-order kinetics (i.e., the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher.

Renal excretion of unchanged medicine depends upon urinary pH. As urinary pH rises above 6,5, the renal clearance of free salicylate increases from < 5 % to > 80 %.

Following therapeutic doses, approximately 10 % is found excreted in the urine as salicylic acid, 75 % as salicyluric acid, 10 % phenolic- and 5 % acyl-glucuronides of salicylic acid.

Based on the pharmacokinetic and metabolic characteristics of both compounds, clinically significant PK interactions are unlikely.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Castor oil, Hydrogenated

Cellulose, microcrystalline

Hydroxypropyl cellulose

Iron oxide yellow

Mannitol

Polyethylene glycol-6000

Silica, colloidal hydrated

Stearic acid

Film coating (Opadry II yellow 32K520181)

Hypromellose

Iron Oxide Yellow

Lactose Monohydrate

Titanium Dioxide

Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below at or below 25°C.

Keep blisters in the carton until required for use.

6.5 Nature and contents of container

Alu-Alu blister packed in a printed outer carton.

Pack size: 30.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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9. DATE OF FIRST AUTHORISATION

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