Professional information for ESOCID OTC

SCHEDULING STATUS: S2

1. NAME OF THE MEDICINE

ESOCID OTC 20 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains esomeprazole magnesium dihydrate equivalent to 20 mg esomeprazole.

Excipients with known effect:

Contains sugar.

Each tablet contains 19,3 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablets.

Pink coloured, oval shaped, biconvex, bevelled edge, film-coated tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ESOCID OTC is indicated for the temporary, short-term relief of heartburn and hyperacidity.

4.2 Posology and method of administration

Posology:

ESOCID OTC may be taken once daily at a maximum daily dose of 20 mg (one ESOCID OTC tablet) for a maximum treatment period of 14 days.

Special populations:

Impaired renal function:

Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution.

Impaired hepatic function:

Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum daily dose of 20 mg ESOCID OTC should be used.

Elderly:

Dose adjustment is not required in the elderly.

Paediatric population:

ESOCID OTC should not be used in children younger than 1 year since no data is available.

Method of administration:

Oral.

The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed.

4.3 Contraindications

- Hypersensitivity to esomeprazole, substituted benzimidazoles or to any of the excipients of ESOCID OTC (see section 6.1).
- Concomitant administration of ESOCID OTC with atazanavir or nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

ESOCID OTC is not indicated for mild gastrointestinal complaints, such as nervous dyspepsia.

Prior to treatment or 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, the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded, as the treatment with ESOCID OTC may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Concomitant administration of clopidogrel and esomeprazole resulted in decreased exposure to the active metabolite of clopidogrel by an average of 40 %. The maximum inhibition of (ADP induced) platelet aggregation decreased by an average of 14 %. Based on these data, concomitant use of ESOCID OTC and clopidogrel should be avoided.

During treatment with antisecretory medicines, serum gastrin increases in response to the decreased acid secretion. Also, chromogranin A (CgA) increase due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference, the esomeprazole treatment should be temporarily stopped 5 days before CgA measurements.

There is an increased risk of subclinical acute interstitial nephritis (AIN) associated with proton pump inhibitors (PPIs), such as ESOCID OTC, which may progress to acute kidney injury and/or chronic renal failure.
Symptoms of interstitial nephritis may persist even when treatment with the PPI is terminated.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like ESOCID OTC, 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 dysrhythmia 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, including ESOCID OTC, with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting ESOCID OTC treatment and periodically during treatment.

Risk of fracture

Proton pump inhibitors, including ESOCID OTC, 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.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping ESOCID OTC. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

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

Clostridium difficile is a bacterium that can cause severe debilitating diarrhoea that does not improve. Symptoms may include watery stools, abdominal pain, fever, and patients may develop more serious intestinal conditions.

Sucrose:

ESOCID OTC contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take ESOCID

OTC.

4.5 Interaction with other medicines and other forms of interaction

Effects of ESOCID OTC on the pharmacokinetics of other medicines:

The gastric acid suppression during treatment with ESOCID OTC, might decrease or increase the absorption of medicines with a gastric pH-dependent absorption. The absorption of medicines such as ketoconazole, itraconazole and erlotinib can decrease while the absorption of medicines such as digoxin can increase during treatment with ESOCID OTC.

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10 % (up to 30 % in 2 out of 10 subjects). Digoxin toxicity has been reported. Caution should be exercised when ESOCID OTC is given at high doses in elderly patients. Therapeutic monitoring of digoxin levels should be done.

ESOCID OTC inhibits CYP2C19, the major ESOCID OTC metabolising enzyme. Concomitant administration of 30 mg ESOCID OTC resulted in a 45 % decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance. Concomitant administration of 40 mg ESOCID OTC resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients.

Concomitant administration of 40 mg ESOCID OTC to warfarin-treated patients showed that, despite elevation in the trough plasma concentration of the less potent *R*-isomer of warfarin, the coagulation times were within the accepted range.

From post marketed use, cases of elevated international normalised ratio (INR) of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when warfarin is co-administered with ESOCID OTC at initiation of treatment, during the treatment and at ending treatment.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic

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 %. Based on these data, concomitant use of ESOCID OTC and clopidogrel should be avoided.

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 metabolites by 29 % and 69 %, respectively. ESOCID OTC can be suspected to have a similar effect.

In concomitant administration of 40 mg ESOCID OTC resulted in a 32 % increase in area under the plasma concentration-time curve (AUC) and a 31 % prolongation of elimination half-life ($t_{½}$) but no significant increase in peak plasma levels of cisapride. This interaction did not alter the influence of cisapride on cardiac electrophysiology.

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 ESOCID OTC may need to be considered.

ESOCID OTC has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Studies evaluating concomitant administration of ESOCID OTC and either naproxen (non-selective NSAID) or rofecoxib (COX-2-selective NSAID) did not identify any clinically relevant interaction.

Concomitant administration of ESOCID OTC may significantly reduce the plasma levels of atazanavir.

Omeprazole has been reported to interact with some antiretroviral medicines. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral medicines. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral medicines, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended.

Co-administration of esomeprazole (40 mg once daily) reduced mean nelfinavir exposure by approximately 40 % and the mean exposure of the pharmacological active metabolite was reduced by approximately 75 – 90 %. ESOCID OTC substantially decreases the concentration of nelfinavir. Concomitant administration with esomeprazole and antiretroviral medicines such as atazanavir and nelfinavir is not recommended.
For other antiretroviral medicines, such as saquinavir, increased serum levels have been reported of 80 – 100 %. There are also some antiretroviral medicines for which unchanged serum levels have been reported when given with omeprazole. Close monitoring or dose alteration is recommended.

Tipranavir may decrease the concentration of ESOCID OTC. Co-administration is not recommended. However, if used concurrently, the dose of ESOCID OTC should be increased.

Effects of other medicines on the pharmacokinetics of ESOCID OTC:
ESOCID OTC is metabolised by CYP2C19 and CYP3A4. Concomitant administration of ESOCID OTC and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to ESOCID OTC.
Concomitant administration of ESOCID OTC and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than tripling of the ESOCID OTC exposure.
Dose adjustment of ESOCID OTC is not required.

Medicines 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:

Safety during pregnancy has not been established.

Breastfeeding:

Safety during lactation has not been established.

4.7 Effects on ability to drive and use machines

ESOCID OTC may cause dizziness and blurred vision, thereby affecting the ability to drive or use machinery.

4.8 Undesirable effects

a) Summary of the safety profile

Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical trials (and also from post-marketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations.

b) Summary of the adverse reactions

Blood and lymphatic system disorders

Less frequent: leukopenia, thrombocytopenia

Immune system disorders

Less frequent: hypersensitivity reactions (e.g. angioedema and anaphylactic reaction/shock)

Metabolism and nutrition disorders

Less frequent: peripheral oedema, hyponatraemia, hypomagnesaemia

Frequency unknown: Severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.

Psychiatric disorders

Less frequent: insomnia, agitation, confusion, depression, aggression, hallucination

Nervous system disorders

Frequent: headache

Less frequent: dizziness, paraesthesia, somnolence, taste disturbance

Eye disorders

Less frequent: blurred vision

Ear and labyrinth disorders

Less frequent: vertigo

Respiratory, thoracic and mediastinal disorders

Less frequent: bronchospasm

Gastrointestinal disorders

Frequent: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation, fundic gland polyps (benign)

Less frequent: dry mouth, stomatitis, gastrointestinal candidiasis, gastrointestinal infections, microscopic colitis

Hepatobiliary disorders

Less frequent: increased liver enzymes, hepatitis with or without jaundice, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Less frequent: dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity

Frequency unknown: subacute cutaneous lupus erythematosus

Musculoskeletal and connective tissue disorders

Less frequent: arthralgia, myalgia, muscular weakness

Renal and urinary disorders

Less frequent: interstitial nephritis may progress to acute kidney injury and/or chronic renal failure; in some patients, renal failure has been reported concomitantly

Reproductive system and breast disorders

Less frequent: gynaecomastia

General disorders and administration site conditions

Less frequent: malaise, hyperhidrosis.

Post-marketing experience:

Blood and lymphatic system disorders:

Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia.

Immune system disorders:

Hypersensitivity reactions, e.g. angioedema and anaphylactic reaction/shock.

Metabolism and nutrition disorders:

Peripheral oedema, hyponatraemia.

Psychiatric disorders:

Insomnia, agitation, confusion, depression, aggression, hallucination.

Nervous system disorders:

Headache, dizziness, paraesthesia, somnolence, taste disturbance.

Eye disorders:

Blurred vision.

Ear and labyrinth disorders:

Vertigo.

Respiratory, thoracic and mediastinal disorders:

Bronchospasm.

Gastrointestinal disorders:

Abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation, dry mouth, stomatitis, gastrointestinal candidiasis.

Hepatobiliary disorders:

Increased liver enzymes, hepatitis with or without jaundice, hepatic encephalopathy, hepatic failure.

Skin and subcutaneous tissue disorders:

Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN).

Musculoskeletal and connective tissue disorders:

Arthralgia, myalgia, muscular weakness.

Renal and urinary disorders:

Interstitial nephritis.

Reproductive system and breast disorders:

Gynaecomastia.

General disorders and administration site conditions:

Malaise, hyperhidrosis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ESOCID OTC is important. It allows continued monitoring of the benefit/risk balance of ESOCID OTC. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No specific antidote is known. ESOCID OTC is extensively plasma protein bound and is therefore not readily dialysable. 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: Drugs for acid-related disorders, proton pump inhibitor.

ATC code: A02B C05.

Mechanism of action:

Esomeprazole, the *S*-isomer of omeprazole, reduces gastric acid secretion through specific inhibition of the acid pump in the parietal cell, where it is concentrated and converted to the active

form in the acidic environment of the secretory canaliculi and inhibits the enzyme H^+K^+-ATPase – the acid pump. This effect on the final step of the gastric acid secretion is dose-dependent and provides for effective inhibition of 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 1 hour. After repeated administration of 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 gastro-oesophageal reflux disease (GORD) patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours were 76 %, 54 % and 24 %, respectively, for esomeprazole 20 mg. Corresponding proportions for esomeprazole 40 mg were 97 %, 92 % and 56 %, respectively.

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

Food intake had no significant influence on the effect of esomeprazole on intragastric acidity.

Other effects related to acid inhibition:

During long-term treatment with antisecretory medicines, gastric glandular cysts occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

5.2 Pharmacokinetic properties

Absorption:

Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the *R*-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1 – 2 hours after dose. The absolute bioavailability is 89 % after repeated once daily administration. For 20 mg esomeprazole the corresponding values are 50 % and 68 %, respectively.

Food intake both delays and decreases the absorption of esomeprazole, although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution:

The apparent volume of distribution at steady state in healthy subjects is approximately 0,22 litres/kg body weight. Esomeprazole is 97 % plasma protein bound.

Metabolism:

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.

Elimination:

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

Total plasma clearance is about 17 litres per hour after a single dose and about 9 litres per hour 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 compound is found in urine.

Special populations:

Poor metabolisers:

Approximately 2,9 % ± 1,5 % 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 esomeprazole.

Hepatic insufficiency:

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction 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 dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing.

Renal insufficiency:

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.

Gender:

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 dosage of esomeprazole.

Elderly:

The metabolism of esomeprazole is not significantly changed in elderly subjects (71 – 80 years of age).

Paediatric population:

Following repeated dose administration of 20 mg and 40 mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma concentration (t_{max}) in 12- to 18-year-olds was similar to that in adults for both esomeprazole doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Copovidone

Crospovidone

Glycerol monostearate

Hydroxypropyl cellulose (E463)

Hypromellose (E464)

Magnesium oxide, light

Magnesium stearate (E572)

Mannitol (E421)

Methacrylic acid ethyl acrylate polymer

Microcrystalline cellulose [E460(i)]

Microcrystalline cellulose, silicified [E460(i)]

Polyethylene glycol 8000

Polysorbate 80 (E433)

Povidone

Sugar spheres

Talc (E553b)

Triethyl citrate (E1505).

Coating:

Opadry Pink [containing hydroxypropyl cellulose (E463), hypromellose (E464), iron oxide red (E172), talc (E553b) and titanium dioxide (E171)].

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in a dry place.

Keep the blister strips in the outer carton until required for use.

Keep out of reach of children.

6.5 Nature and contents of container

Silver aluminium/aluminium blister strips placed in an outer carton with a desiccant. Each blister strip contains 7 tablets.

Pack size: 14 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBER

50/11.4.3/0898

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

04 August 2022

10. DATE OF REVISION OF THE TEXT

02 February 2024