PROFESSIONAL INFORMATION

SCHEDULING STATUS **S2**

1. NAME OF THE MEDICINE

OMIFLYNT 20 mg (Gastro-resistant tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each OMIFLYNT gastro-resistant tablet contains esomeprazole magnesium dihydrate equivalent to 20 mg esomeprazole.

Excipient(s) with known effect:

Each OMIFLYNT tablet contains sugar spheres (sucrose + glucose 16,13 mg).

3. PHARMACEUTICAL FORM

Gastro-resistant tablet.

OMIFLYNT: Light pink oval gastro-resistant tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology:

The recommended dose is 20 mg (one tablet) per day. The duration of treatment is up to 2 weeks.

Once complete relief of symptoms has occurred, treatment should be discontinued.

If no symptom relief is obtained within 2 weeks of continuous treatment, the patient should be instructed to consult a doctor.

Special populations:

Children:

Safety and efficacy have not been established.

Elderly:

Dose adjustment is not required.

Impaired renal function:

Dose adjustment is not required; however, patients with severe renal insufficiency should be treated with caution (see section 5.2).

Impaired hepatic function:

Dose adjustments are not required in patients with mild to moderate liver impairment, however, for patients with severe liver impairment, a maximum daily dose of 20 mg OMIFLYNT is recommended.

Method of administration:

OMIFLYNT should be swallowed whole with liquid. OMIFLYNT should not be chewed or crushed.

4.3 Contraindications

- Hypersensitivity to esomeprazole, to substituted benzimidazoles or to any of the excipients of OMIFLYNT (see section 6.1).
- OMIFLYNT must not be used concomitantly with atazanavir and nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

General:

Patients should be instructed to consult a doctor:

- 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 OMIFLYNT may alleviate symptoms and delay diagnosis.
- If they have had previous gastric ulcer or gastrointestinal surgery.
- If they have been on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks.
- If they have jaundice or severe liver disease.
- If they are aged over 55 years with new or recently changed symptoms.

Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Patients over 55 years taking any non-prescription indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.

Patients should not take OMIFLYNT* as *a long-term preventative medicine:

Treatment with proton pump inhibitors may lead to slightly increased risk of gastric intestinal infections such as *Salmonella* and *Campylobacter* and possibly *Clostridium difficile* (see section 5.1).

PPI therapy like esomeprazole as in OMIFLYNT may be associated with an increased risk of *Clostridium difficile* associated with watery diarrhoea, stomach pain and fever, especially in hospitalised patients. Patients should consult their doctor before taking this medicine if they are due to have an endoscopy or urea breath test.

Combination with other medicines:

Co-administration of OMIFLYNT with atazanavir is contra-indicated (see sections 4.3 & 4.5).

OMIFLYNT is a CYP2C19 inhibitor. When starting or ending treatment with OMIFLYNT, the potential for interactions with medicines metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and OMIFLYNT (see section 4.5).

The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

Patients should not take another PPI or H_2 antagonist concomitantly.

Interference with laboratory tests:

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, OMIFLYNT treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Subacute cutaneous lupus erythematosus (SCLE):

Proton pump inhibitors are associated with very infrequent cases of 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 OMIFLYNT. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

OMIFLYNT is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

Renal impairment:

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking esomeprazole and may occur at any point during esomeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

OMIFLYNT should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Sugar warning:

OMIFLYNT contains sucrose and glucose, which may have an effect on the glycaemic control of patients with diabetes mellitus.

OMIFLYNT contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption syndrome, or sucrase-isomaltase insufficiency should not take OMIFLYNT.

4.5 Interaction with other medicines and other forms of interaction

Effects of OMIFLYNT on the pharmacokinetics of other medicines:

As esomeprazole is one enantiomer of omeprazole it is reasonable to advise about interactions reported with omeprazole.

Protease inhibitors:

Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19.

Atazanavir and nelfinavir:

Esomeprazole decreases the concentration of atazanavir and nelfinavir. Co-administration of OMIFLYNT and atazanavir or nelfinavir is contra-indicated (see section 4.3).

For saquinavir (with concomitant ritonavir), increased serum levels (80 to 100 %) have been reported during concomitant omeprazole treatment (40 mg once a day). Treatment with omeprazole 20 mg once a day had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg once a day had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg once a day had no effect on the exposure of lopinavir (with concomitant ritonavir).

Methotrexate:

When given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration, a temporary withdrawal of OMIFLYNT may need to be considered.

Tacrolimus:

Concomitant administration of OMIFLYNT has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dose of tacrolimus adjusted if needed.

Medicines with pH dependent absorption:

Gastric acid suppression during treatment with OMIFLYNT and other PPIs might decrease or increase the absorption of medicines with a gastric pH-dependent absorption. As with other medicines that decrease intragastric acidity, the absorption of medicines such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with OMIFLYNT.

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). Digoxin toxicity has been rarely reported. However, caution should be exercised when OMIFLYNT is given at high doses in elderly patients. Therapeutic monitoring of digoxin should then be reinforced.

Medicines metabolised by CYP2C19:

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with medicines metabolised by CYP2C19 such as diazepam, citalopram, imipramine, clomipramine, phenytoin, etc., the plasma concentrations of these medicines may be increased, and a dose reduction could be needed. This should be considered especially when prescribing OMIFLYNT for on-demand therapy.

Esomeprazole induces the expressions of CYP1A2, thereby increasing the clearance of imipramine, several antipsychotic medicines, tacrine and theophylline.

Diazepam:

Concomitant administration of 30 mg esomeprazole resulted in a 45 % decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin:

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 OMIFLYNT is introduced or withdrawn.

Voriconazole:

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC_{τ} by 15 % and 41 %, respectively.

Cilostazol:

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.

Cisapride:

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). This interaction did not alter the influence of cisapride on cardiac electrophysiology.

Warfarin:

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 OMIFLYNT treatment during treatment with warfarin or other coumarin derivatives.

Clopidogrel:

Studies in healthy subjects have shown that concomitant use of esomeprazole and clopidogrel resulted in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition.

An increase in cardiovascular events has also been reported. Concomitant use of OMIFLYNT and clopidogrel should be avoided.

Investigated medicines with no clinically relevant interaction:

Amoxicillin and quinidine:

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

Naproxen or rofecoxib:

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

Effects of other medicines on the pharmacokinetics of OMIFLYNT:

Medicines which inhibit CYP2C19 and/or CYP3A4:

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of OMIFLYNT and a CYP3A4 inhibitor, clarithromycin (500 mg twice a day (b.i.d.)), 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 OMIFLYNT is not regularly required in either of these situations.

Medicines which induce CYP2C19 and/or CYP3A4:

Medicines known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John’s wort (*Hypericum perforatum*)) may lead to decreased OMIFLYNT serum levels by increasing the esomeprazole metabolism.

Paediatric population:

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety in pregnancy has not been established.

Breastfeeding:

It is unknown whether esomeprazole/metabolites are excreted in human milk. There is insufficient information on the effects of esomeprazole in newborns/infants. OMIFLYNT should not be used during breastfeeding.

Fertility:

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

4.7 Effects on ability to drive and use machines

OMIFLYNT may cause somnolence, dizziness and blurred vision. As concentration may be impaired, patients should be advised to exercise caution when driving or operating machinery (see section 4.8).

4.8 Undesirable effects

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) for esomeprazole. In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

Tabulated list of adverse reactions

System Organ Class	**Frequent**	**Less Frequent**	**Frequency Unknown**
Infections and infestations		*Clostridium difficile* associated diarrhoea.	
Blood and lymphatic system disorders		Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia.	
Immune system disorders		Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock.	
Metabolism and nutrition disorders		Peripheral oedema, hyponatraemia.	Hypomagnesaemia, severe hypomagnesaemia can correlate with hypocalcaemia, hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders		Insomnia, agitation, confusion, depression, aggression,	

		hallucinations.	
Nervous system disorders	Headache.	Dizziness, paraesthesia, somnolence, taste disturbance.	
Eye disorders		Blurred vision.	
Ear and labyrinth disorders:		Vertigo.	
Respiratory, thoracic and mediastinal disorders		Bronchospasm, sinusitis, respiratory infection.	
Gastrointestinal disorders:	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign).	Dry mouth, stomatitis, gastrointestinal candidiasis.	Microscopic colitis.
Hepatobiliary disorders		Increased liver enzymes, hepatitis with or without jaundice, hepatic encephalopathy in patients with pre-existing liver disease, hepatic failure.	

Skin and subcutaneous tissue disorders		Dermatitis, pruritus, rash, urticaria, alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN).	Subacute cutaneous lupus erythematosus (see section 4.4).
Musculoskeletal and connective tissue disorders		Arthralgia, myalgia, muscular weakness.	
Renal and urinary disorders		Tubulointerstitial nephritis (with possible progression to renal failure).	
Reproductive system and breast disorders		Gynaecomastia.	
General disorders and administration site conditions		Fatigue, malaise, increased sweating.	

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. Health care providers 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.

Suspected adverse reactions can also be reported directly to the Holder of the Certificate of Registration (HCR) via the link: https://pvi1j.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com.

4.9 Overdose

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg esomeprazole were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole 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

Pharmacological classification: A 11.4.3 Medicines acting on gastro-intestinal tract. Other

5.1 Pharmacodynamic properties

Esomeprazole is a proton pump inhibitor that requires activation in an acid environment. After absorption into the systemic circulation, it diffuses into the parietal cells of the stomach and accumulates in the acidic secretory canaliculi. 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.

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. Here, it is activated by proton-

catalysed formation of a tetracyclic sulfenamide, trapping the compound so it cannot diffuse back across the canalicular membrane.

The activated form then binds covalently with sulfhydryl groups of cysteines in the H^+/K^+-ATPase, where it inhibits the enzyme H^+K^+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

Acid secretion resumes only after a new pump molecule is synthesised and inserted into the luminal membrane, providing a prolonged suppression of acid secretion. Because proton pump inhibitors block the final step in acid production, esomeprazole is effective in acid suppression.

Pharmacodynamic effects:

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 five days, mean peak acid output after pentagastrin stimulation is decreased 90 % when measured 6 to 7 hours after dosing on day five.

After five 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 GORD 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:

Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78 % of patients after four weeks, and in 93 % after eight weeks.

One week treatment with esomeprazole 20 mg twice daily and appropriate antibiotics, results in successful eradication of *H. pylori* in approximately 90 % of patients.

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory medicines for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

In a randomised, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding characterised as Forrest Ia, Ib, IIa or IIb (9 %, 43 %, 38 % and 10 % respectively) were randomised to receive esomeprazole solution for infusion (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72-hour period, all patients received open-label 40 mg oral esomeprazole for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5,9 % in the esomeprazole treated group compared to 10,3 % for the placebo group. At 30 days post-treatment, the occurrence of rebleeding in the esomeprazole treated versus the placebo treated group was 7,7 % vs 13,6 %.

During treatment with antisecretory medicines, 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.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

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, Campylobacter* and in hospitalised patients, possibly also *Clostridium difficile*.

Clinical efficacy:

In two studies with ranitidine as an active comparator, esomeprazole showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.

In two studies with placebo as comparator, esomeprazole showed better effect in the prevention of gastric and duodenal ulcers in patients using NSAIDs (aged > 60 and/or with previous ulcer), including COX-2 selective NSAIDs.

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 1,6 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 area under the plasma concentration curve (AUC) is increased three-fold when the dose is increased from 20 mg to 40 mg, and the C_{max} also increases proportionally with increase in dose.

The AUC after administration of a single 40 mg dose of esomeprazole is decreased by 33 % to 53 % after food intake compared to fasting conditions.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.
Esomeprazole should be taken at least half an hour before meals.

Distribution:

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.

Biotransformation:

Esomeprazole is completely metabolised in the liver by the cytochrome P-450 system (CYP). The metabolites lack anti-secretory activity. 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 sulfone, 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 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1 to 1,5 hours after repeated once-daily dosing.

The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg b.i.d. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC 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 medicine is found in urine.

Linearity/non-linearity:
The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg twice daily. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC 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.

Special patient populations:

Poor metabolisers:
Approximately 1 to 2 % 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.

Elderly:

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

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 posology of esomeprazole.

Hepatic impairment:

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 daily dose 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 impairment:

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.

Paediatric population:

Adolescents 12 to 18 years:

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Sugar spheres (composed of sucrose, maize starch and liquid glucose)

Hydroxypropylcellulose

Povidone

Talc

Titanium dioxide (E171)

Methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30 %

Glycerol monostearate 40 to 55 *Type II*

Propylene glycol

Stearic acid *Type 50*

Polysorbate 80

Simeticone

Microcrystalline cellulose

Macrogol 6000

Crospovidone *Type A*

Silica colloidal anhydrous

Magnesium stearate

Tablet coating:

Hypromellose

Macrogol 6000

Titanium dioxide (E171)

Talc

Ferric oxide red (E172)

Ferric oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

OMIFLYNT is available in Aluminium (soft)/Aluminium (hard) blister cards or bottles (polyethylene bottles) closed with polypropylene caps with desiccant inserts in packs of 14 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBER

OMIFLYNT: 44/11.4.3/0335

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 June 2013

10. DATE OF REVISION OF THE TEXT

13 August 2025

[1]Company Reg. No.: 1990/001979/07