SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

NEXMEZOL 20 (tablets)

NEXMEZOL 40 (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each NEXMEZOL 40 gastro-resistant tablet contains esomeprazole magnesium dihydrate equivalent to 40 mg esomeprazole.

Each NEXMEZOL 20 tablet contains sugar spheres (sucrose + glucose 16,13 mg).

Each NEXMEZOL 40 tablet contains sugar spheres (sucrose + glucose 32,26 mg).

3. PHARMACEUTICAL FORM

NEXMEZOL 20: Light pink oval film-coated tablet.

NEXMEZOL 40: Pink oval film-coated tablet with a score line on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- **Gastro-Oesophageal Reflux Disease (GORD):**
    - Treatment of erosive reflux oesophagitis.
    - Long-term management of patients with healed oesophagitis to prevent relapse.
    - Symptomatic treatment of gastro-oesophageal reflux disease (GORD).

• **As a treatment adjunct for:**

- Treatment of duodenal ulcers associated with *Helicobacter pylori* infection.
- Reduction of risk of peptic ulcer recurrence in patients with *Helicobacter pylori* associated ulcers.

4.2 Posology and method of administration

• **Gastro-Oesophageal Reflux Disease (GORD):**

- ***Erosive reflux oesophagitis:***

  40 mg once daily for 4 weeks. For those who have not healed in the 4 weeks, an additional 4 weeks treatment is recommended.

- ***Management of patients with healed oesophagitis to prevent relapse:***

  20 mg once daily.

- ***Symptoms associated with gastro-oesophageal reflux disease (GORD) – in patients without oesophagitis:***

  20 mg once daily in patients without oesophagitis. For patients whose symptoms have not been controlled after the 4 week period, a further investigation should be carried out. 20 mg once daily may be taken when necessary, once symptoms have resolved.

• **As a treatment adjunct for:**

- Treatment of duodenal ulcers associated with *Helicobacter pylori* infection.
- Reduction of risk of peptic ulcer recurrence in patients with *Helicobacter pylori* associated ulcers:

Triple therapy regimen of NEXMEZOL 20 mg twice daily, clarithromycin 500 mg twice daily and amoxicillin 1000 mg twice daily for 7 days is recommended.

If symptom control has not been achieved after four weeks of treatment with the prescribed daily dose, further investigation is recommended.

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.

Impaired hepatic function:

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

Method of administration:

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

4.3 Contraindications

Hypersensitivity to esomeprazole, to substituted benzimidazoles or to any of the excipients of NEXMEZOL.

NEXMEZOL must not be used concomitantly with atazanavir and nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

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 NEXMEZOL may alleviate symptoms and delay diagnosis.

Long-term use:

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

On demand treatment:

Patients on on-demand treatment should be instructed to contact their doctor if their symptoms change in character.

***Helicobacter pylori* eradication:**

When prescribing NEXMEZOL for eradication of *Helicobacter pylori*, possible interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other medicines metabolised via CYP3A4, such as cisapride.

Gastrointestinal infections:

Treatment with NEXMEZOL may lead to slightly increased risk of gastrointestinal infections such as *Salmonella,* and *Campylobacter* (see section 5.1).

Absorption of vitamin B12:

NEXMEZOL, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with

reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Hypomagnesaemia:

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like NEXMEZOL for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take NEXMEZOL with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting NEXMEZOL treatment and periodically during treatment.

Risk of fracture:

Proton pump inhibitors, especially if used in high doses and over long durations (> 1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10 to 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.

Combination with other medicines:

Co-administration of NEXMEZOL with atazanavir is not recommended (see sections 4.3 & 4.5).

NEXMEZOL is a CYP2C19 inhibitor. When starting or ending treatment with NEXMEZOL, the potential for interactions with medicines metabolised through CYP2C19 should be considered.

An interaction is observed between clopidogrel and NEXMEZOL (see section 4.5).

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

When prescribing NEXMEZOL for on-demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of NEXMEZOL should be considered (see section 4.5).

Interference with laboratory tests:

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, NEXMEZOL 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 NEXMEZOL. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

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

Sugar warning:

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

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

4.5 Interaction with other medicines and other forms of interaction

Effects of NEXMEZOL on the pharmacokinetics of other medicines:

Protease inhibitors:

Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75 % decrease in AUC, C_{max} and C_{min}). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once per day (qd)) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30 % in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg qd without omeprazole 20 mg qd. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, C_{max} and C_{min} by 36 to 39 % and mean AUC, C_{max} and C_{min} for the pharmacologically active metabolite M8 was reduced by 75 to 92 %.

Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with NEXMEZOL and atazanavir is not recommended and concomitant administration with NEXMEZOL and nelfinavir is contraindicated (see section 4.3 and 4.4).

For saquinavir (with concomitant ritonavir), increased serum levels (80 to 100 %) have been reported during concomitant omeprazole treatment (40 mg qd). Treatment with omeprazole 20 mg qd had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg qd had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg qd 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 NEXMEZOL may need to be considered.

Tacrolimus:

Concomitant administration of NEXMEZOL 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 NEXMEZOL 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 NEXMEZOL.

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 NEXMEZOL 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 NEXMEZOL 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 NEXMEZOL 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).

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 NEXMEZOL treatment during treatment with warfarin or other coumarin derivatives.

Clopidogrel:

Results from studies in healthy subjects have shown a pharmacokinetic (PK)/ pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg orally 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 %.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + acetylsalicylic acid (ASA) 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40 % of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of clopidogrel should be discouraged.

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 NEXMEZOL:

Medicines which inhibit CYP2C19 and/or CYP3A4:

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of NEXMEZOL 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 NEXMEZOL is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

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 NEXMEZOL serum levels by increasing the esomeprazole metabolism.

Paediatric population:

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy:

Clinical data on exposed pregnancies with NEXMEZOL are insufficient. With the racemic mixture, omeprazole, data on a larger number of exposed pregnancies from epidemiological studies indicate no malformative nor foetotoxic effect. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

A moderate amount of data on pregnant women (between 300 to 1000 pregnancy outcomes)

indicates no malformative or foeto/neonatal toxicity of esomeprazole.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Breastfeeding:

It is unknown whether esomeprazole/metabolites are excreted in human milk. There is insufficient information on the effects of esomeprazole in newborns/infants. NEXMEZOL 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

NEXMEZOL has minor influence on the ability to drive and use machines. Adverse reactions such as dizziness and visual disturbances are uncommon (see section 4.8). If affected, patients should not drive or use machines.

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.

Blood and lymphatic system disorders:

***Less frequent*:** Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia.

Immune system disorders:

***Less frequent*:** Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock.

Metabolism and nutrition disorders:

***Less frequent*:** Peripheral oedema, hyponatraemia.

***Not known*:** Hypomagnesaemia (see section 4.4), severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.

Psychiatric disorders:

***Less frequent*:** Insomnia, agitation, confusion, depression, aggression, hallucinations.

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, sinusitis, respiratory infection.

Gastrointestinal disorders:

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

***Less frequent*:** Dry mouth, stomatitis, gastrointestinal candidiasis.

***Not known*:** Microscopic colitis.

Hepatobiliary disorders:

Less frequent: Increased liver enzymes, hepatitis with or without jaundice, hepatic failure, encephalopathy in patients with pre-existing liver disease.

Not known: Subacute cutaneous lupus erythematosus (see section 4.4).

Skin and subcutaneous tissue disorders:

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

Musculoskeletal and connective tissue disorders:

Less frequent: Arthralgia, myalgia, muscular weakness.

Renal and urinary disorders:

Less frequent: Interstitial nephritis, 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, increased sweating.

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.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in both children and adults during long-term treatment with esomeprazole.

The findings are considered to be of no clinical significance.

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

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

Paediatric population:

In a study in paediatric GORD patients (< 1 to 17 years of age) receiving long-term PPI treatment, 61 % of the children developed minor degrees of ECL cell hyperplasia with no known clinical significance and with no development of atrophic gastritis or carcinoid tumours.

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. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

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) (only present in NEXMEZOL 20).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in original package at or below 25 °C.

6.5 Nature and contents of container

NEXMEZOL is available in Aluminium (soft)/Aluminium (hard) blister cards or bottles (polyethylene bottles) closed with polypropylene caps with desiccant inserts in packs of 14 or 28.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

72 Steel Road

Spartan

Kempton Park

1619

8. REGISTRATION NUMBERS

NEXMEZOL 20: 44/11.4.3/0335

NEXMEZOL 40: 44/11.4.3/0336

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 June 2013

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Namibia	Nexmezol 20	NS2	13/11.4.3/0210
	Nexmezol 40	NS2	13/11.4.3/0211
Botswana	Nexmezol 20	S2	BOT1702975
	Nexmezol 40	S2	BOT1702976
Zambia	Nexmezol 20	POM	039/099
	Nexmezol 40	POM	039/100
Zimbabwe	Nexmezol 20	PIM	2018/16.7/5627
	Nexmezol 40	P.P	2018/16.7/5628

ATC Code: A02BC05, Proton Pump Inhibitors

Name and address of manufacturer:

Salutas Pharma GmbH

Otto-von-Guericke-Allee-1

D-39179, Barleben,

Germany

10. DATE OF REVISION OF THE TEXT

03 July 2020

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