SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

MITOGUT 40 (Lyophilized powder for solution for injection and infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MITOGUT 40:

Each vial contains esomeprazole sodium equivalent to esomeprazole 40 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lyophilized powder for solution for injection and infusion.

MITOGUT 40: A white to off-white cake or powder filled in 5 ml clear glass USP type I vials sealed with a bromobutyl rubber stopper and flip-off aluminium seal with polypropylene green button.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MITOGUT 40 is indicated for Gastroesophageal Reflux Disease as an alternative where oral therapy is not appropriate and for the shortest possible time.

Gastroesophageal reflux disease:

- Treatment of erosive reflux oesophagitis
- Long-term management of patients with healed oesophagitis to prevent relapse
- Treatment of severe symptoms of reflux disease

MITOGUT 40 is indicated for the short-term maintenance of haemostasis and prevention of

rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

4.2 Posology and method of administration

Posology

Adults:

Gastroesophageal Reflux Disease (GORD):

Treatment with MITOGUT 40 can be given for up to 7 days as part of a full treatment period for the specified indications. When oral therapy is appropriate or possible, intravenous therapy with MITOGUT 40 should be discontinued and the therapy should be continued orally.

Treatment of erosive reflux oesophagitis:

40 mg once daily.

The duration of treatment should be 4 weeks. An additional 4 weeks treatment is recommended for patients in whom the oesophagitis has not healed or who have persistent symptoms.

Long term management of patients with healed oesophagitis to prevent relapse and treatment of severe symptoms of reflux disease:

20 mg once daily.

Maintenance of haemostasis and prevention of rebleeding of gastric or duodenal ulcers:

80 mg administered as bolus infusion over 30 minutes followed by a continuous intravenous infusion of 8 mg/hr given over 3 days.

The parenteral treatment period should be followed by acid-suppression therapy with esomeprazole 40 mg once daily for 4 weeks.

Method of administration

For preparation of reconstituted solution, see section 6.6.

Injection (40 mg vial):

40 mg dose:

The reconstituted solution should be given as an intravenous injection over a period of at

least 3 minutes.

20 mg dose:

Half of the reconstituted solution should be given as an intravenous injection over a period of approximately 3 minutes.

Infusion (40 mg vial):

40 mg dose:

The reconstituted solution should be given as an intravenous infusion over a period of 10-30 minutes.

20 mg dose:

Half of the reconstituted solution should be given as an intravenous infusion over a period of 10-30 minutes.

80 mg bolus dose:

The reconstituted solution containing 80 mg esomeprazole should be given as an intravenous infusion over a period of 30 minutes.

8 mg/hour dose:

The reconstituted solution should be given as a continuous intravenous infusion over a period of 71,5 hours (calculated rate of infusion of 8 mg/hr).

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:

Gastroesophageal Reflux Disease (GORD):

Dose adjustment is not required in patients with mild to moderate liver impairment (Child-Pugh class A, B). For patients with severe liver impairment (Child-Pugh class C), a maximum daily dose of 20 mg MITOGUT 40 should not be exceeded.

Bleeding ulcers:

Dose adjustment is not required in patients with mild to moderate liver impairment. For

patients with severe liver impairment, following an initial bolus dose of 80 mg MITOGUT 40, a continuous intravenous infusion dose of 4 mg/hour may be sufficient to maintain adequate acid control.

Elderly:

In the elderly, dose adjustment is not required.

4.3 Contraindications

MITOGUT 40 is contra-indicated in patients with known hypersensitivity to esomeprazole, substituted benzimidazole or any other ingredients of the formulation.

Concomitant use with nelfinavir and atazanavir.

4.4 Special warnings and precautions for use

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, melaena or haematemesis) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with MITOGUT 40 may alleviate symptoms and delay diagnosis.

The concomitant administration of MITOGUT 40 with medicines such as atazanavir and nelfinavir is contraindicated. See section 4.3 and section 4.5.

During concomitant treatment with warfarin, therapeutic medicine monitoring is recommended.

Acute Tubulointerstitial Nephritis

Acute tubulointerstitial nephritis is characterised by an inflammatory reaction within the tubulointerstitial space of the kidney. Acute interstitial inflammatory reactions are associated with damage to the tubulointerstitium, leading to acute kidney injury.

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia). Discontinue MITOGUT 40 and evaluate patients with suspected acute TIN.

Other effects related to acid inhibition:

During treatment with MITOGUT 40, serum gastrin increases, in response to the decreased acid secretion.

Gastric glandular cysts occur during long-term treatment with oral esomeprazole. These changes are a physiological consequence of pronounced inhibition of acid secretion, appear to be reversible and are benign.

Gastrointestinal infections:

Decreased gastric acidity due to any means including proton pump inhibitors such as MITOGUT 40 increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with MITOGUT 40 may lead to increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and also possibly *Clostridium difficile* in hospitalised patients.

Absorption of vitamin B_{12}:

MITOGUT 40 may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption on long-term therapy.

Hypomagnesaemia:

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like MITOGUT 40 for at least 3 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.

If patients are expected to be on prolonged MITOGUT 40 treatment, or given MITOGUT 40 with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting MITOGUT 40 treatment and periodically during treatment.

Subacute cutaneous lupus erythematosus (SCLE):

Proton pump inhibitors, such as MITOGUT 40, are associated with 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 discontinuation of MITOGUT 40 treatment should be considered. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Risk of fracture:

MITOGUT 40, especially if used in high doses and after long durations (> 1 year), increases the risk of hip, wrist and spine fracture, predominantly in the elderly or in the 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 developing osteoporosis should be appropriately managed and they should have an adequate intake of vitamin D and calcium.

Clopidogrel:

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with MITOGUT 40, the potential for interactions with medicines metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole. Concomitant use of MITOGUT 40 and clopidogrel should be discouraged, since the clinical relevance of this interaction is uncertain (see section 4.5).

Chromogranin A (CgA) measurements:

MITOGUT 40 treatment may lead to an increased CgA level and interfere with investigations for neuroendocrine tumours. MITOGUT 40 treatment should be discontinued for at least 5 days before CgA measurements, in order to avoid this interaction. If CgA and gastrin levels have not returned to reference range after the initial measurement, measurements should be repeated 14 days after MITOGUT 40 treatment has been discontinued.

Children:

MITOGUT 40 should not be used in children since no data is available.

4.5 Interaction with other medicines and other forms of interaction

Effects of MITOGUT 40 on the pharmacokinetics of other medicines:

Protease inhibitors:

Omeprazole has been reported to interact with some antiretroviral medicines. 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 antiretroviral medicine. Other possible interaction mechanisms are via inhibition of 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. For other antiretroviral medicines, such as saquinavir, increased serum levels have been reported.

There are also some antiretroviral medicines for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with MITOGUT 40 and antiretroviral medicines such as atazanavir and nelfinavir is contraindicated (see section 4.3).

Methotrexate:

There have been reports of increased methotrexate levels in some patients when PPIs were co-administered with methotrexate. In high-dose methotrexate administration, a temporary withdrawal of MITOGUT 40 may need to be considered.

Tacrolimus:

Concomitant administration of esomeprazole with tacrolimus 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 it may be necessary to adjust the dosage of tacrolimus.

Medicines with pH dependent absorption:

Gastric acid suppression during treatment with MITOGUT 40 might decrease or increase the absorption of medicines with a gastric pH dependent absorption.

During treatment with MITOGUT 40, the absorption of ketoconazole, itraconazole, and erlotinib can decrease and the absorption of digoxin can increase. Caution should be exercised when MITOGUT 40 is given at high doses in elderly patients. Therapeutic medicinal product monitoring of digoxin should then be reinforced.

Medicines metabolised by CYP2C19:

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when MITOGUT 40 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.

Diazepam:

Concomitant oral administration of 30 mg esomeprazole resulted in a 45 % decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

Phenytoin:

Concomitant oral administration of 40 mg esomeprazole and phenytoin resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients; dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with MITOGUT 40 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:

MITOGUT 40 acts as a CYP2C19 inhibitor and may increase AUC for cilostazol and one of its active metabolites.

Warfarin:

Concomitant oral administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketed use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending concomitant MITOGUT 40 treatment with warfarin or other coumarin derivatives.

Clopidogrel:

Clopidogrel given concomitantly with esomeprazole has shown a pharmacokinetic

(PK)/pharmacodynamic (PD) interaction between clopidogrel and esomeprazole.

Concomitant use of MITOGUT 40 with clopidogrel should be discouraged, as inconsistent data is available with regards to the clinical implications of this PK/PD interaction on cardiovascular events (see section 4.4).

Effects of other medicines on the pharmacokinetics of MITOGUT 40:

Medicines which inhibit CYP2C19 and/or CYP3A4:

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant oral administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of MITOGUT 40 and a combined inhibitor of CYP3A4 and CYP2C19, such as voriconazole may result in more than doubling of the esomeprazole exposure. However, dose adjustment is not required for MITOGUT 40 in either of these situations.

In patients with severe hepatic impairment, and if long-term treatment is indicated, dose adjustment should be considered.

Medicines which induce CYP2C19 and/or CYP3A4:

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

Investigated medicines with no clinically relevant interaction:

Amoxicillin or 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.

4.6 Fertility, pregnancy and lactation

Limited clinical data on exposed pregnancies are available for esomeprazole. Caution should be exercised when prescribing MITOGUT 40 to pregnant women.

It is not known whether esomeprazole is excreted in human breast milk.

There is insufficient information on the effects of MITOGUT 40 in newborns/infants.

Therefore, MITOGUT 40 should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

MITOGUT 40 may cause dizziness and blurred vision and may affect the ability to drive or use machines.

4.8 Undesirable effects

Blood and lymphatic system disorders:

Less frequent: Leucopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders:

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

Metabolism and nutritional disorders:

Less frequent: Peripheral oedema, hyponatraemia

Frequency unknown: Hypomagnesaemia (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, tinnitus

Cardiac disorders:

Frequency unknown: Angina, tachycardia, bradycardia

Respiratory, thoracic and mediastinal disorders:

Less frequent: Bronchospasm, coughing

Gastrointestinal disorders:

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

Less frequent: Dry mouth, stomatitis, gastrointestinal candidiasis, pancreatitis

Frequency unknown: Microscopic colitis

Hepato-biliary disorders:

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

Skin and subcutaneous tissue disorders:

Frequent: Administration site reactions*

Less frequent: Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity, Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous eruption

Frequency not known: Exacerbation of vitiligo, subacute cutaneous lupus erythematosus

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthralgia, myalgia, muscular weakness, fractures of the hip, wrist or spine, back pain

Renal and urinary disorders:

Less frequent: Interstitial nephritis: in some patients, renal failure has been reported concomitantly. Interstitial nephritis may progress to renal failure as it is not necessarily reversed when treatment is discontinued.

Reproductive system and breast disorders:

Less frequent: Gynaecomastia, impotence

General disorders and administration site conditions:

Less frequent: Malaise, hyperhidrosis, fatigue

*Administration site reactions have mainly been observed in a study with high dose exposure over 3 days (72 hours). In a non-clinical programme for esomeprazole intravenous formulation there was no evidence of vaso-irritation but a slight tissue inflammatory reaction at the injection site after subcutaneous (paravenous) injection was noted. The non-clinical findings somewhat indicated that the clinical tissue irritation was concentration related.

Irreversible visual impairment has been reported in isolated cases of critically ill patients who have received omeprazole (the racemate) intravenous injection, especially at high doses, but no causal relationship has been established.

4.9 Overdose

Intravenous doses of 308 mg MITOGUT 40 over 24 hours and single oral doses of 80 mg were uneventful. No specific antidote is known.

Due to extensive protein binding, esomeprazole is not readily dialysable. TREATMENT IS SYMPTOMATIC AND SUPPORTIVE.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A 11.4.3 Medicines acting on the gastrointestinal tract. Other.

Esomeprazole is the S-isomer of the proton pump inhibitor omeprazole.

Esomeprazole reduces gastric acid secretion through inhibition of the enzyme H^+K^+-ATPase, the acid pump in the parietal cell, where it is concentrated and converted to the active form in the acidic environment of the acid canaliculi. This effect on the final step of the gastric acid secretion is dose-dependent and inhibitory for basal and stimulated acid secretion.

Using Area Under the Curve (AUC) as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown, after oral administration of esomeprazole.

During intravenous administration of 80 mg esomeprazole as a bolus infusion over minutes followed by continuous intravenous infusion of 8 mg/hr for 23,5 hours, intragastric pH above 4, and pH above 6 was maintained for a mean time of 21 hours, and 11-13 hours, respectively, over 24 hours in healthy subjects.

5.2 Pharmacokinetic properties

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 and excretion:

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

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

After a single dose, total plasma clearance is about 17 litres/hour and after repeated administration, about 9 litres /hour. After repeated once-daily dosing, the plasma elimination half-life is about 1,3 hours. The area under the plasma concentration-time curve increases in a non-linear fashion with repeated administration of esomeprazole. Esomeprazole is completely eliminated from plasma between doses. There is no tendency for accumulation during once daily administration.

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

Special patient populations:

Elderly:

In elderly subjects (71 - 80 years of age), the metabolism of esomeprazole is not significantly changed.

Gender:

Following a single oral 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. Similar differences have been seen for intravenous administration of esomeprazole. These findings have no implications for the dosage of esomeprazole.

Renal impairment:

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

Hepatic impairment:

In patients with severe liver impairment (Child-Pugh C), there is a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in GORD (Gastroesophageal Reflux Disease) patients with severe liver impairment. For patients with bleeding ulcers and severe liver impairment, following an initial bolus dose of 80 mg, a maximum continuous intravenous infusion of 4 mg/hr may be sufficient in patients with bleeding ulcers. There is no tendency for esomeprazole or its major metabolites to accumulate with once-daily dosing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate

Sodium hydroxide

6.2 Incompatibilities

The degradation of the reconstituted solution is highly pH dependent and the product must therefore only be reconstituted with 0,9 % sodium chloride for intravenous use according to the instructions above. The reconstituted solution should not be mixed or co-administered in the same infusion set with any other medicine.

6.3 Shelf life

2 years.

Reconstituted solution for injection and infusion:

Chemical, physical and microbiological in-use stability of the reconstituted solution has been demonstrated for 12 hours in 0,9 % sodium chloride solution for intravenous use. The reconstituted solution can be stored at up to 30 °C.

Although the chemical and physical stability of the reconstituted product has been proven for

12 hours, both the reconstituted or diluted product should be used immediately.

6.4 Special precautions for storage

MITOGUT 40 should be stored at or below 25 °C in the outer container, which it is provided in, since this protects the vial from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

MITOGUT 40: Cartons containing 10 clear glass USP type I vials.

6.6 Special precautions for disposal and other handling

Injection (40 mg vial):

The solution for injection is prepared by adding 5 ml of 0,9 % sodium chloride for intravenous use to the vial.

Infusion (40 mg vial):

The solution for infusion is prepared by dissolving the contents of one vial in up to 100 ml of 0,9 % sodium chloride for intravenous use.

Continuous infusion (40 mg vial):

The solution for infusion is prepared by dissolving the contents of 2 vials of esomeprazole 40 mg in up to 100 ml of 0,9 % sodium chloride for intravenous use.

On reconstitution, a colourless to pale yellow solution is formed.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

47/11.4.3/0800

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