Docusign Envelope ID: E08F7841-EB08-8C41-81D7-07765DE10CF0

TOPZOLE RANGE – PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TOPZOLE® 20 Enteric-coated tablets

TOPZOLE® 40 Enteric-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TOPZOLE® 20 Each tablet contains 22,6 mg pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole and is sugar-free.

TOPZOLE® 40 Each tablet contains 45,1 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole and is sugar-free.

Excipient with known effect (**TOPZOLE® 20 and TOPZOLE® 40):**

Excipient with known effect (**TOPZOLE® 20,** Enteric-coated Tablets**):**

Each tablet contains 21,33 mg of mannitol and 3,40 mg sodium.

Excipient with known effect (**TOPZOLE® 40,** Enteric-coated Tablets**):**

Each tablet contains 42,70 mg of mannitol and 6,79 mg of sodium.

For the full list of excipients, see **Section 6.1**

3. PHARMACEUTICAL FORM

TOPZOLE® 20: Yellow, oval, biconvex enteric-coated tablet with a white to off-white core, imprinted "P20" on one side.

TOPZOLE® 40: Yellow, oval, biconvex enteric-coated tablet, with a white to off-white core, imprinted "P40" on one side.

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4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TOPZOLE® 40 is indicated for the short-term treatment of duodenal ulcer, gastric ulcer and reflux oesophagitis. If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori* infection, **TOPZOLE® 40** used in combination with appropriate antibiotics may be useful.

TOPZOLE® 40 is indicated for the treatment of Zollinger-Ellison Syndrome.

TOPZOLE® 20 is indicated for the symptomatic improvement (e.g. heartburn, acid regurgitation, pain on swallowing) and healing of mild gastro-oesophageal reflux disease. In patients with healed reflux disease, recurring symptoms can be controlled using an on-demand regimen of 20 mg once daily when required.

TOPZOLE® 20 is indicated for long-term management and prevention of relapse in gastro-oesophageal reflux disease.

TOPZOLE® 20 is indicated for the prevention of gastroduodenal lesions and dyspeptic symptoms induced by non-selective non-steroidal anti-inflammatory drugs (NSAID's) in patients at risk, and with a need for continuous NSAID treatment.

4.2 Posology and method of administration

TOPZOLE® 20 and **TOPZOLE® 40** should be swallowed whole with a little water either before or during breakfast.

Duodenal ulcer

The recommended oral dose is **40 mg TOPZOLE®** once daily for 2 to 4 weeks. If the duodenal ulcer has been demonstrated to be associated with *Helicobacter pylori* infection, **TOPZOLE® 40** used in combination with appropriate antibiotics may be useful.

Gastric ulcer

The recommended oral dose is **40 mg TOPZOLE®** once daily for 4 to 8 weeks.

In the case of a suspected gastric ulcer, malignancy of the gastric ulcer should be excluded, as treatment could conceal the symptoms and may delay diagnosis.

Reflux oesophagitis

The recommended oral dose is **40 mg TOPZOLE®** once daily for 4 to 8 weeks.

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Zollinger-Ellison Syndrome

For management of Zollinger-Ellison Syndrome patients should start their treatment with a daily dose of 80 mg (2 tablets of **TOPZOLE® 40**). Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion as a guide. With doses above 80 mg daily, the dose should be divided and given twice daily.

Mild Gastro-oesophageal reflux disease

The recommended oral dose is **20 mg TOPZOLE®** per day. A 4-week period is usually required for healing of mild gastro-oesophageal reflux disease. If this is not sufficient, healing will usually be achieved within a further 4 weeks. In patients with healed reflux disease, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily when required.

Long-term management and prevention of relapse in gastro-oesophageal reflux disease

For long-term management a maintenance dose of one **TOPZOLE® 20** tablet per day is recommended, increasing to **40 mg TOPZOLE®** per day if a relapse occurs. After healing of the relapse, the dose can be reduced to **20 mg TOPZOLE®**. Experience with long-term administration is limited.

For prevention of gastro-duodenal lesions and dyspeptic symptoms induced by non-selective non- steroidal anti-inflammatory drugs (NSAID's) in patients at risk and with a need for continuous NSAID treatment, the recommended oral dose is one **TOPZOLE® 20** tablet per day.

Elderly patients

No dosage adjustment is necessary in the elderly.

Impaired renal function

No dosage adjustment is required in the presence of impaired renal function.

In addition, **TOPZOLE ® 40** must not be used in combination treatment for eradication of *H. pylori* in patients with impaired renal function, since currently no data are available on the efficacy and safety of **TOPZOLE ®** in combination treatment for these patients.

Impaired hepatic function

A daily dose of **20 mg TOPZOLE®** should not be exceeded in patients with mild to moderate liver impairment (see **Section 5.2 and Section 4.4**). In addition, **TOPZOLE® 40** must not be used in combination treatment for eradication of *H. pylori* in patients with mild to moderate hepatic dysfunction, since currently no data are available on the efficacy and safety of **TOPZOLE®** in combination treatment for these patients.

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4.3 Contra-indications

Hypersensitivity to pantoprazole and any of the excipients.

Safety and efficacy in children have not been established.

Severely impaired liver function (**see Section 4.4**).

TOPZOLE®, should not be co-administered with nelfinavir & atazanavir **(see Section 4.5).**

4.4 Special warnings and precautions for use

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

Further investigation is to be considered if symptoms persist despite adequate treatment.

The daily dose of **40 mg TOPZOLE®** should not be exceeded in elderly patients or in those with impaired renal function.

Bone fracture

PPI therapy, including **TOPZOLE®**, may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received daily doses, and long-term **TOPZOLE®** therapy (a year or longer).

Clostridium difficile

PPI therapy, like **TOPZOLE®**, may be associated with an increased risk of *Clostridium difficile*-associated diarrhoea, especially in hospitalised patients. This diagnosis should be considered for diarrhoea that does not improve **(see Section 4.8).**

Hypomagnesaemia

Hypomagnesaemia has been reported in patients treated with **TOPZOLE®** for more than three months (in most cases after a year of therapy). Serious consequences of hypomagnesaemia include tetany, dysrhythmia and seizure.

HIV Protease Inhibitors

Co-administration of **TOPZOLE®** is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, nelfinavir due to a significant reduction in their bioavailability (**see Section 4.5**).

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Methotrexate

Concomitant use with high dose methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities (**see Section 4.5).**

Severe Cutaneous Adverse Reactions (SCAR)

Severe cutaneous adverse reactions, including erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs (see Undesirable Effects, 4.8). Discontinue pantoprazole at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

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 healthcare professional should consider stopping **TOPZOLE®**. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, **TOPZOLE®** 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.

TOPZOLE® contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

Mannitol

Patients with the rare hereditary condition of mannitol intolerance should not take **TOPZOLE®**.

Hepatic impairment

In patients with mild to moderate liver impairment the liver enzymes should be monitored regularly during treatment with **40 mg TOPZOLE®**, particularly on long-term use. In the case of a rise of the liver enzymes **TOPZOLE®** should be discontinued**.**

Use of **TOPZOLE® 20** as preventative of gastroduodenal ulcers, induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications.

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TOPZOLE® is not indicated for mild gastro-intestinal complaints such as nervous dyspepsia.

Gastric malignancy

Symptomatic response to **TOPZOLE®** does not preclude the presence of gastric malignancy.

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

Influence on Vitamin B_{12} absorption

Daily treatment with any acid blocking medicines, including **TOPZOLE®**, over a long period of time (e.g., longer than 3 years) may lead to malabsorption of vitamin B_{12} caused by hypo- or achlorhydia. Cases of vitamin B_{12} deficiency under acid-blocking therapy have been reported in the literature. This should be considered when respective clinical symptoms are observed.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant intake of food has no influence on the bioavailability.

The active ingredient of **TOPZOLE®** is metabolised in the liver via the cytochrome P450 enzyme system. An interaction of **TOPZOLE®** with other medicines or compounds which are metabolised using the same enzyme system cannot be excluded.

No clinically significant interactions were, however, observed in specific tests with a number of such medicines or compounds, namely antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenprocoumon, phenytoin, piroxicam, theophylline, warfarin and oral contraceptives.

Warfarin

The response to warfarin may be affected by any concomitant medication. It is therefore good practice to monitor the patient with additional PT (prothrombin time) /INR (international normalised ratio) determinations when **TOPZOLE®** is initiated, discontinued or taken irregularly.

Due to long lasting inhibition of gastric acid secretion **TOPZOLE®** may reduce the of absorption of medicines with a gastric pH-dependent bioavailability, e.g. some azole antifungals like ketoconazole, itraconazole, posaconazole and other medicines like erlotinib.

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HIV Protease Inhibitors

Co-administration of pantoprazole is contraindicated with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, and nelfinavir; due to significant reduction in their bioavailability (see Contraindications, 4.3).

There were no interactions with concomitantly administered antacids.

Methotrexate

Concomitant use of **TOPZOLE®** with methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities (**see Section 4.4**).

Coumarin Anticoagulants (Phenprocoumon or Warfarin)

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the

pharmacokinetics of warfarin, phenprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly.

Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Effects of Other Medicines on Pantoprazole

Drugs that Inhibit or Induce CYP2C19

Inhibitors of CYP2C19, such as fluvoxamine, would likely increase the systemic exposure to pantoprazole. Inducers of CYP2C19 may decrease the systemic exposure to pantoprazole.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and during lactation has not been established.

4.7 *Effects on ability to drive and use machines*

Pantoprazole is not expected to adversely affect the ability to drive or use machines.

However, adverse drug reactions such as dizziness and visual disturbances (e.g., blurred vision) may occur (**see Section 4.8**). If affected, patients should not drive or operate machines.

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4.8 Undesirable effects

SIDE EFFECTS

Very common (≥1/10); common (≥1/100, < 1/10); uncommon (≥1/1000, < 1/100); rare (≥ 1/10 000, < 1/1000) very rare (≤ 1/10 000) including isolated cases, not known (cannot be estimated from the available data).

MEDRA System Organ Class	**Frequency**				
	Common	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders			Agranulocytosis	Thrombocytopenia; Leukopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia; Hypomagnesaemia (see section 4.4); Hypocalcaemia(1); Hypokalaemia(1)
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)
Nervous system disorders		Headache; Dizziness	Taste disorders		Paraesthesia
Eye disorders			Disturbances in vision / blurred vision		

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Gastrointestinal disorders	Fundic gland polyps (benign)	Diarrhoea; Nausea / vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			Microscopic colitis
Hepatobiliary disorders		Liver enzymes increased (transaminases, γ-GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and subcutaneous tissue disorders		Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Toxic epidermal Necrolysis; Lyell syndrome; Drug reaction with eosinophilia and systemic symptoms; Acute generalized exanthematous pustulosis; Erythema multiforme; Photosensitivity; Subacute cutaneous lupus erythematosus (see section 4.4); Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders		Fracture of the hip, wrist or spine (see section 4.4)	Arthralgia; Myalgia		Muscle spasm[2]

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Renal and urinary disorders					Tubulointerstitial nephritis (TIN) with possible progression that may lead to chronic renal failure)
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions		Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

1. Hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see section 4.4)

2. Muscle spasm as a consequence of electrolyte disturbance

Post-marketing reports:

***Hepatobiliary disorders*:** Hepatocellular injury, jaundice, hepatocellular failure

***Psychiatric disorders*:** Hallucination, confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)

***Renal and urinary disorders*:** Interstitial nephritis

***Skin and subcutaneous tissue disorders*:** Stevens-Johnson syndrome, Lyell syndrome (Toxic epidermal necrolysis), erythema multiforme, photosensitivity

***Infections and infestations*:** *Clostridium difficile*-associated diarrhoea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who umc.org) found on SAHPRA website. Additionally, suspected adverse reactions can be reported to AE.SouthafricaSSA@takeda.com or on the 24 hours contact number: 082 525 3040

4.9 Overdose

There are no known symptoms of overdosage in man. No specific therapeutic recommendation can be made in cases of overdosage.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

A 11.4.3 Medicines acting on the gastro-intestinal tract.

Mechanism of Action

Pantoprazole is a proton pump inhibitor, i.e., it inhibits specifically and dose-proportionally H^+,K^+-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

Pantoprazole is a substituted benzimidazole which accumulates in the acidic compartment of the parietal cells after absorption. In the parietal cell it is protonated and chemically re-arranged to the active inhibitor, a cyclic sulphenamide, which binds to the H^+,K^+-ATPase, thus inhibiting the proton pump and causing suppression of stimulated and basal gastric acid secretion after single and multiple intravenous and oral pantoprazole dosing. Because pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus.

Pantoprazole exerts its full effect in a strongly acidic environment (pH<3) and remains mostly inactive at higher pH values, which explains its selectivity for the acid secreting parietal cells of the stomach. Therefore, the complete pharmacological and therapeutic effect for pantoprazole can only be achieved in the acid-secreting parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

Effect on gastric acid secretion

Following oral or intravenous administration, pantoprazole inhibits the pentagastrin-stimulated gastric acid secretion. The mean acid inhibition was 85 %, 2½ to 3½ hours after dosing with pantoprazole 40 mg/day for 7 days.

After stopping the administration of pantoprazole, there is no evidence of rebound hypersecretion and 7 days after administering the last dose the acid output is normal.

Pantoprazole maintains the physiological pH rhythm. The values, however, are shifted to higher levels. During the night, periods with pH values approximating placebo have been found to occur.

Although pantoprazole has a half-life of approximately 1 hour, the antisecretory effect increases during repeated once daily administration, demonstrating that the duration of action markedly exceeds the serum elimination half-life.

5.2 Pharmacokinetic properties

Absorption and distribution

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Oral:

Pantoprazole is unstable in acid and is administered orally in the form of an enteric-coated tablet. Absorption takes place in the small intestine. On average, the maximum plasma concentrations are approximately 2 to 3 µg/ml about 2½ hours after administration of 40 mg pantoprazole daily, as a single or multiple dose in healthy volunteers. The absolute systemic bioavailability of pantoprazole from single and multiple oral doses of pantoprazole is approximately 77 %.

The plasma kinetics for pantoprazole after both oral and intravenous administration are linear over the dose range 10-80 mg.

Metabolism

Pantoprazole is almost exclusively metabolised in the liver. The main metabolite is desmethylpantoprazole, which is conjugated with sulphate.

Elimination

Renal elimination represents the most important route of excretion (approximately 80 %) for the metabolites of pantoprazole. The balance is excreted with the faeces. The half-life of the main metabolite is approximately 1½ hours which is slightly longer than that of pantoprazole.

Pharmacokinetic profile in patients with impaired liver or renal function

For patients with mild to moderately severe hepatic cirrhosis the elimination half-life values increase to between 7 to 9 hours. The AUC values increase by a factor of 5 to 8, while the maximum serum concentration only increases by a factor of 1,5 in comparison with healthy subjects.

In patients with renal impairment the half-life of the main metabolite is moderately increased but there is no accumulation at therapeutic doses. The half-life of pantoprazole in patients with renal impairment is comparable to the half-life of pantoprazole in healthy subjects. Pantoprazole is poorly dialysed. A slight increase in AUC and C_{max} occurs in elderly volunteers compared with younger people.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

TOPZOLE® 20

Excipients include: sodium carbonate, mannitol, crospovidone, polyvidone K90, calcium stearate, hypromellose 2910, polyvidone K25, titanium dioxide, yellow ferric oxide, propylene glycol, methacrylic acid-ethyl and triethyl citrate.

TOPZOLE® 40

Excipients include: sodium carbonate, mannitol, crospovidone, polyvidone K90, calcium stearate, hypromellose 2910, polyvidone K25, titanium dioxide, yellow ferric oxide, propylene glycol, methacrylic acid-ethyl and triethyl citrate.

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6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines except those mentioned in **Section 6.6**.

6.3 Shelf life

TOPZOLE® 20 and 40: 3 years.

6.4 Special precautions for storage

Store at or below 30 ˚C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

TOPZOLE® 20 Tablets in white plastic bottle fitted with grey screw closure and attached bellows-type spacer, in quantities of 28 tablets or in printed silver aluminium foil blister packs of 28 tablets.

TOPZOLE® 40 Tablets in white plastic bottle fitted with grey screw closure and attached bellows-type spacer, in quantities of 14 and 28 tablets or in printed silver aluminium foil blister packs of 14 and 28 tablets.

6.6 Special precautions for disposal and other handling

General precautions

Procedures for proper handling and disposal of medicines should be considered.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

TAKEDA (Pty) Ltd

Building A,

Monte Circle

64 Montecasino Boulevard

Fourways

2191

South Africa

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8. REGISTRATION NUMBER(S)

TOPZOLE 20: 38/11.4.3/0061

TOPZOLE 40: 38/11.4.3/0060

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 April 2013

10. DATE OF REVISION OF THE TEXT

20 February 2026