1. NAME OF THE MEDICINAL PRODUCT
Pantoprazole Sandoz Gastro-resistant Tablets 40 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each gastro-resistant tablet contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate).

Excipient:
Each gastro-resistant tablet contains 2 µg of the colouring agent Ponceau 4R aluminium lake (E124) per gastro-resistant tablet.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Gastro-resistant tablet.
A yellow, oval coated tablet.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
- In combination with two appropriate antibiotics (see Dosage) for the eradication of *H. pylori* in patients with peptic ulcers with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism.
- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux oesophagitis

4.2 Posology and Method of Administration
Tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

Reflux oesophagitis
One tablet of Pantoprazole 40 mg per day. In individual cases, the dose may be doubled (increase to 2 tablets Pantoprazole 40 mg daily) especially when there has been no response to other treatment. A 4-week period is usually required for the treatment of reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Eradication of Helicobacter pylori in combination with two appropriate antibiotics
In *Helicobacter pylori* positive patients with gastric and duodenal ulcers, eradication of the germ by a combination therapy should be achieved. Considerations should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance and the appropriate use and prescription of antibacterial agents. Depending upon the resistance pattern, the following combinations can be recommended for the eradication of *Helicobacter pylori*:

a) twice daily one tablet Pantoprazole 40 mg
+ twice daily 1000 mg amoxicillin
+ twice daily 500 mg clarithromycin

b) twice daily one tablet Pantoprazole 40 mg
+ twice daily 500 mg metronidazole
+ twice daily 500 mg clarithromycin

c) twice daily one tablet Pantoprazole 40 mg
+ twice daily 1000 mg amoxicillin
+ twice daily 500 mg metronidazole

In combination therapy for eradication of *Helicobacter pylori* infection, the second Pantoprazole 40 mg tablet should be taken 1 hour before the evening meal. The combination therapy is implemented for 7 days in general and can be prolonged for a further 7 days to a total duration of up to two weeks. If, to ensure healing of the ulcers, further treatment with pantoprazole is indicated, the dose recommendations for duodenal and gastric ulcers should be considered.

If combination therapy is not an option, e.g. if the patient has tested negative for *Helicobacter*

pylori, the following dose guidelines apply for Pantoprazole 40 mg monotherapy:

Treatment of gastric ulcer
One tablet of Pantoprazole 40 mg per day. In individual cases, the dose may be doubled (increase to 2 tablets Pantoprazole 40 mg daily) especially when there has been no response to other treatment. A 4-week period is usually required for the treatment of gastric ulcers. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Treatment of duodenal ulcer
One tablet of Pantoprazole 40 mg per day. In individual cases, the dose may be doubled (increase to 2 tablets Pantoprazole 40 mg daily) especially when there has been no response to other treatment. A duodenal ulcer generally heals within 2 weeks. If a 2-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Special Patient Populations
Pediatric patients
The experience in children is limited. Pantoprazole 40 mg tablet is not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group.

Hepatic impairment
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment (see section 4.4).

In addition, pantoprazole 40 mg tablet must not be used in combination treatment (e.g. amoxicillin, clarithromycin,) for eradication of *H. pylori* in patients with moderate to severe hepatic dysfunction since currently no data are available on the efficacy and safety of pantoprazole in combination treatment of these patients (see section 4.3).

Renal impairment
No dose adjustment is necessary in patients with impaired renal function.

In addition, pantoprazole 40 mg tablet must not be used in combination treatment (e.g. amoxicillin, clarithromycin) for eradication of *H. pylori* in patients with impaired renal function, since currently no data are available on the efficacy and safety of pantoprazole in combination treatment for these patients.

Elderly patients
Generally, no dose adjustment is necessary in elderly patients. However, the daily dose of 40 mg should not be exceeded in treatment of gastric or duodenal ulcer.

4.3 Contraindications
Hypersensitivity to the active substance, substituted benzimidazoles, or to any of the other excipients of Pantoprazole 40 mg or of the combination partners.

Pantoprazole 40 mg must not be used in combination treatment for eradication of *H. pylori* in patients with moderate to severe liver or kidney function disturbances since currently no data are available on the efficacy and safety of Pantoprazole 40 mg in combination treatment for these patients.

Pantoprazole, like other PPIs, should not be co-administered with atazanavir (see section 4.5).

4.4 Special warnings and special precautions for use
Pantoprazole is not indicated for mild gastro-intestinal complaints such as nervous dyspepsia.

Hepatic Impairment
In patients with severe liver impairment, the daily dose has to be reduced to 20 mg pantoprazole. In patients with severe liver impairment, the liver enzymes should be monitored during therapy regularly. In the case of a rise of the liver enzymes, the treatment should be discontinued (see section 4.2).

Combination therapy
In the case of combination therapy, the summaries of product characteristics of the respective

medicinal products should be observed.

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

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

Influence on vitamin B12 absorption
Daily treatment with any acid-suppressing medication over a prolonged period of time (several years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Cyanocobalamin deficiency should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, individuals with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if relevant clinical symptoms are observed.

Long-term treatment
In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Gastrointestinal infections caused by bacteria, including Clostridium difficile
Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with Pantoprazole 40 mg may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella and Campylobacter.* In hospitalized patients, PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Published observational studies suggest that proton pump inhibitor (PPI) therapy like pantoprazole may be associated with an increased risk of *Clostridium difficile*-associated diarrhoea (CDAD), especially in hospitalised patients. This diagnosis should be considered for diarrhoea that does not improve (see section 4.8). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with pantoprazole, refer to Warnings and Precautions sections of those package inserts.

Hypomagnesemia
Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious manifestations of hypomagnesamia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmias can occur but they may begin insidiously and be overlooked. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia. In most patients, treatment of hypomagnesemia (and hypomagnesemia associated hypocalcemia and/or hypokalemia) required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically (see section 4.8).

Bone Fractures
Several published observational studies suggest that proton pump inhibitor (PPI) therapy 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 high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE)
Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving Pantoprazole Sandoz gastro-resistant tablets, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., Antinuclear antibody) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Concomitant use with Methotrexate
Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients (see section 4.5).

HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, nelfinavir; due to significant reduction in their bioavailability.

Interference with Laboratory Tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, proton pump inhibitor treatment should be stopped 14 days before CgA measurements.

This medicinal product contains colouring agent Ponceau 4R aluminium lake (E 124), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction
Drugs with pH-Dependent Absorption Pharmacokinetics
Pantoprazole may reduce or increase the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole).

HIV medications (atazanavir)
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, nelfinavir; due to significant reduction in their bioavailability.

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore PPIs, including pantoprazole, should not be co-administered with atazanavir (see section 4.3).

Coumarin anticoagulants (phenprocoumon or warfarin)
Although no interaction during concomitant administration of phenprocoumon or warfarin has

been observed in clinical pharmacokinetic studies, a few isolated cases of changes in International Normalised Ratio (INR) and prothrombin have been reported during concomitant treatment in the post-marketing period. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients treated with coumarin anticoagulants (e.g. phenprocoumon or warfarin), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

Methotrexate
Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted (see section 4.4).

Other interactions studies
Pantoprazole is extensively metabolized in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

An interaction of pantoprazole with other drugs or compounds which are metabolized using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in interaction studies with drugs also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin and an oral contraceptive containing levonorgestrel and ethinyl oestradiol.

Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption of digoxin.

There were no interactions with concomitantly administered antacids.

Interaction studies have also been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

Clopidogrel
Concomitant administration of pantoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of pantoprazole.

Drugs that Inhibit or Induce CYP2C19
Inhibitors of CYP2C19, such as fluvoxamine, would likely increase the systemic exposure of pantoprazole. Inducers of CYP2C19 may decrease the systemic exposure to pantoprazole.

4.6 Pregnancy and lactation
Pregnancy
The limited data from the use of pantoprazole in pregnant women does not indicate foetal/ neonatal toxicity. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Pantoprazole 40 mg should not be used during pregnancy, unless clearly necessary.

Lactation
Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore, a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Pantoprazole 40 mg should be made taking into account the benefit of breastfeeding to the child, and the benefit of Pantoprazole 40 mg therapy to women.

4.7 Effects on ability to drive and use machines
Pantoprazole is not expected to adversely affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected,

patients should not drive or operate machines.

4.8 Undesirable Effects

Approximately 5% of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhoea and headache, both occurring in approximately 1% of patients.

Table 1 lists adverse reactions reported with pantoprazole in clinical studies and post-marketing experience. The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines:

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

For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a “not known” frequency.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency System Organ Class	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Very rare** (<1/10,000)	**Not known**
Blood and lymphatic system disorders		Agranulocytosis	Leukopenia; Thrombocytopenia; Pancytopenia	
Immune system disorders		Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		Systemic lupus erythematosus
Metabolism and nutrition disorders		Hyperlipidaemias; Weight changes		Hyponatraemia; Hypomagnesaemia; Hypocalcaemia*; Hypokalaemia*
Psychiatric disorders	Sleep disorders	Depression	Disorientation	Hallucination; Confusion
Nervous system disorders	Headache; Dizziness	Taste disorders		
Eye disorders		Disturbances in vision/ blurred vision		
Gastrointestinal disorders	Diarrhoea; Nausea; Vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			

Hepatobiliary disorders	Liver enzymes increased	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and subcutaneous tissue disorders	Rash/Exanthema; Eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity; Cutaneous lupus erythematosus; DRESS^
Musculoskeletal and connective tissue disorders		Arthralgia; Myalgia		Fracture of the wrist, hip and spine
Renal and urinary disorders				Interstitial nephritis
Reproductive system and breast disorders		Gynaecomastia		
General disorders and administration site conditions	Asthenia; Fatigue and malaise	Body temperature increased; Peripheral oedema		

* Hypocalcemia and/or hypokalemia may be related to the occurrence of hypomagnesemia (see section 4.4)
^DRESS: Drug Rash with Eosinophilia and Systemic Symptoms

Post-marketing experience
Immune system: systemic lupus erythematosus
Skin and subcutaneous tissue: cutaneous lupus erythematosus

4.9 Overdose
Systemic exposure with doses up to 240 mg administered intravenously over 2 minutes was well tolerated.
As pantoprazole is extensively protein bound, it is not readily dialysable.
In the case of overdose with clinical signs of intoxication, the usual rules of intoxication therapy apply.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties
Pharmacotherapeutic group: Proton pump inhibitors, ATC Code: A02BC02

Mechanism of action
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells. Pantoprazole is converted to its active form in the acidic canaliculi in the parietal cells where it inhibits the H+, K+-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach.

The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved in 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

Since pantoprazole binds to the enzyme distal to the cell receptor level, the substance can affect hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the active substance is given orally or intravenously. The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the normal upper limit. During long-term treatment, gastrin levels

double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments have not been observed in humans.

An influence of a long-term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid and liver enzymes according to results in animal studies.

5.2 Pharmacokinetic Properties

Absorption

After ingestion, pantoprazole is rapidly absorbed into the bloodstream. On average the maximum serum concentrations (C_{max}) of 2 - 3 µg/ml are achieved at about 2 to 2.5 hours after administration. After single and repeated administration of pantoprazole, the pharmacokinetic characteristics of pantoprazole are very similar.

Both oral and I.V. administration of pantoprazole in the dose range of 10 mg to 80 mg result in linear serum pharmacokinetics. The absolute bioavailability from the tablet was found to be about 77%.

Concomitant intake of food had no relevant influence on the AUC or on the maximum serum concentration (C_{max}) and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Distribution

Pantoprazole's serum protein binding is about 98%, and in keeping with this, pantoprazole has a low volume of distribution (about 0.15 l/kg) and limited tissue distribution.

Metabolism

Pantoprazole is rapidly eliminated from the circulation and extensively metabolized in the liver. Metabolism occurs via oxidation by the CYP enzyme system, predominantly by CYP2C19 and CYP3A4 (Phase I metabolism, which is saturable). Pantoprazole undergoes further biotransformation by conjugation with sulphate, which involves the cytoplasmic enzyme sulphotransferase (phase II metabolism, which is not saturable), and which presents the main metabolism of pantoprazole.

Excretion and Elimination

About 80% of the metabolites of pantoprazole are eliminated via the renal route, the rest via the feces. None of the metabolites are considered as biologically active. The main metabolite in both the serum and urine is desmethylpantoprazole, which is conjugated with sulphate. $T_{1/2}$ of the main metabolite is about 1.5 hour (which is not much longer than that of pantoprazole, 1 hour).

Special populations

Impaired renal function

In patients with impaired renal function (including dialysis), pantoprazole showed no prolonged elimination half-life and no accumulation when compared with healthy subjects. No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole can be dialyzed. Although the main metabolite has a moderately delayed half-life (2 - 3h), excretion is still rapid and thus accumulation does not occur.

Impaired hepatic function

Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 3 and 6 h and the AUC values increased by a factor of 3 – 5, the maximum serum concentration only increased slightly by a factor of 1.3 (after oral administration) compared with healthy subjects. A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.

Age, Gender, Race

As with other clinically used PPIs, a small percentage of the population (about 3% Caucasians, 20% Asians) shows slower elimination of pantoprazole ($T_{1/2}$ being up to 10 hours as compared with 1 hour).

Such persons are known as poor metabolizers as a result of a deficiency of the CYP2C19 enzyme. In these individuals, the metabolism of pantoprazole is probably mainly catalyzed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolizers than in subjects having a functional CYP2C19 enzyme (extensive metabolizers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of pantoprazole.

Compared with younger subjects, slight increases in AUC and C_{max} were noted after single and repeated oral administration of pantoprazole to healthy elderly subjects (age >65 years). However, no dose adjustment is generally necessary in elderly patients.

Drug Interactions
Pantoprazole is metabolized in the liver via the CYP enzyme system. An interaction of pantoprazole with other drugs or compounds, which are metabolized using the same enzyme system, cannot be ruled out.

Nevertheless, in specific tests pantoprazole did not affect the clearance of several compounds metabolized by CYP enzymes. Vice-versa, all drugs that were tested regarding their potential influence on the pharmacokinetics of pantoprazole had no relevant effect.

No detectable interactions between pantoprazole and any other commonly prescribed co-medication tested so far were found.

Metabolism of pantoprazole occurs via oxidation by the CYP enzyme system, predominantly by CYP2C19 and CYP3A4. Interaction studies with drugs also metabolized by these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin, and an oral contraceptive containing levonorgestrel and ethinyl estradiol did not reveal clinically significant interactions. Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), or CYP2E1 (such as ethanol), or does not interfere with p-glycoprotein related absorption of digoxin. There were no interactions with concomitantly administered antacids. Interaction studies have also been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found. (See section 4.5).

5.3 *Preclinical Safety Data*
Carcinogenesis, Mutagenesis, Impairment of Fertility
Non-clinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In the two-year carcinogenicity studies in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and it can be concluded that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment. In the two-year rodent studies, an increased number of liver tumors was observed in rats and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.

Animal Toxicology and/or Pharmacology
A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg). The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no harmful effects on the thyroid glands are expected.

In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 3 mg/kg.

Investigations revealed no evidence of impaired fertility or teratogenic effects. Crossing of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core

Calcium stearate
Cellulose microcrystalline
Crospovidone
Hydroxypropylcellulose (type EXF)
Sodium carbonate, anhydrous
Silica, colloidal anhydrous

Coating

Hypromellose
Iron oxide yellow (E172)
Macrogol 400
Methacrylic acid – ethyl acrylate copolymer (1:1)
Polysorbate 80
Ponceau 4R aluminium lake (E124)
Quinoline yellow aluminium lake (E104)
Sodium laurilsulfate
Titanium dioxide (E171)
Triethyl citrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to outer carton.

6.4 Special Precautions for Storage

Store at or below 30ºC.

6.5 Nature and Contents of Container

Al/OPA/Al/PVC blister packaging: 14, 28, 30 tablets.

Not all pack sizes and presentation may be marketed locally.

6.6 Instructions for Use and Handling

No special requirements.

7. PRODUCT REGISTRANT

Novartis (Singapore) Pte Ltd
20 Pasir Panjang Road,
#10-25/28 Mapletree Business City
Singapore 117439

8. DATE OF REVISION OF THE TEXT

Oct 2020