SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCTS

ULSEPAN 40 mg Enteric Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Pantoprazole	40 mg (equivalent to 45.10 mg Pantoprazole sodium sesquihydrate)

Excipients:

Sucrose Stearate	3.80 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Enteric coated tablet.

Yellow colored, oval, biconvex, unscored enteric coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

In adults and children over 12 years of age:

It is indicated in the treatment of gastroesophageal reflux disease.

In adults:

It is used in;

- As combination with appropriate antibiotics for eradication of *Helicobacter pylori (H. pylori)* in duodenal and gastric ulcers associated with this bacteria.
- Peptic ulcer (Gastric and duodenal ulcer),
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.

4.2. Posology and Method of Administration

Posology/Frequency and time of administration:

In adults and children over 12 years of age:

In gastroesophageal reflux disease

Recommended daily dose is one ULSEPAN 40 mg enteric coated tablet. In individual cases the dose may be doubled (two ULSEPAN 40 mg enteric coated tablets daily). Four-week additional treatment may be considered for patients who do not recover in treatment at the end of four weeks.

Adults:

In eradication of *H. pylori* as in a combination with two appropriate antibiotics:

In *H. pylori* positive patients with gastric and duodenal ulcers, combined treatment should be performed to remove the active completely Official local guidelines such as national recommendations should be considered for resistance and prescribing of appropriate antibiotics. Depending upon the resistance patter, the following combinations can be recommended for the eradication of *H. pylori*:

a) One ULSEPAN 40 mg enteric coated tablets twice daily
+ 1000 mg amoxicillin twice daily
+ 500 mg clarithromycin twice daily
b) One ULSEPAN 40 mg enteric coated tablets twice daily
+ 400 – 500 mg metronidazole (or 500 mg tinidazole) twice daily
+ 250 – 500 mg clarithromycin twice daily
c) One ULSEPAN 40 mg enteric coated tablets twice daily
+ 1000 mg amoxicillin twice daily
+ 500 mg metronidazole (or 500 mg tinidazole) twice daily

In combination therapy for eradication of *H. pylori* infection, the second ULSEPAN 40 mg enteric coated tablet should be taken one hour before the evening meal. The combination therapy is implemented for seven days in general and can be prolonged for a further seven days to a total

duration of up to two weeks. If pantoprazole treatment for ulcer treatment is continued, the dose recommendations for duodenal and gastric ulcers should be considered.

In cases that combination therapy is not necessary, e.g. if the patient has tested negative for *H. pylori*, ULSEPAN 40 mg enteric coated tablets monotheraphy is applied in the following dose:

In treatment of gastric ulcer

One ULSEPAN 40 mg enteric coated tablet is taken daily. The dose may be doubled (two ULSEPAN 40 mg enteric coated tablets daily) in individual cases especially when there has been no response to other treatment. A four week period is usually required for the treatment of gastric ulcers. If this time not sufficient, healing will usually be achieved within a further four weeks.

In treatment of duodenal ulcer

One Ulsepan 40 mg enteric coated tablet is taken daily. The dose may be doubled (two ULSEPAN 40 mg enteric coated tablets daily) in individual cases especially when there has been no response to other treatment. A two week period is usually required for the treatment of duodenal ulcers. If this time not sufficient, healing will usually be achieved within a further two weeks in almost all cases.

In Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions

It should be started treatment with 80 mg daily dose (two ULSEPAN 40 mg enteric coated tablets). Thereafter, the dose can be titrated up or down as needed using measurements of gastric acid secretion. When the daily dose is above 80 mg, the dose should be divided twice a day. A temporary increase of the dose above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control. Treatment duration in Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

Administration method:

For oral use.

ULSEPAN should not be chewed or crushed, and should be swallowed whole one hour before a meal with water.

Additional Information Relating to Special Populations:

Renal impairment:

No dose adjustment is necessary in patients with impaired renal function. Combination treatment with ULSEPAN should not be applied for eradication of *H. pylori* in patients with renal impairment since no data are available on the efficacy and safety of combination treatment of ULSEPAN in these patients. (See Section 5.2)

Hepatic impairment:

A daily dose of 20 mg pantoprazole (one ULSEPAN 20 mg) should not be exceeded in patients with severe liver impairment. Combination treatment with ULSEPAN should not be applied for eradication of *H. pylori* in patients with moderate and severe liver impairment since no data are available on the efficacy and safety of combination treatment of ULSEPAN in these patients. (See Section 4.4)

Pediatric population:

It is not recommended to use ULSEPAN in children below 12 years of age since limited data are available on the efficacy and safety in in these age group children. (See Section 5.2)

Geriatric population:

No dose adjustment is necessary in the elderly. (See Section 5.2)

4.3. Contraindications

ULSEPAN should not be used in patients who are known hypersensitivity to the active substance, substituted benzimidazoles, or any of the other excipients which is listed in section 6.1.

4.4. Special Warnings and Precautions for Use

Hepatic Impairment:

In patients with severe liver impairment, the liver enzymes should be monitored regularly during treatment, particularly on long-term use. In the case of a rise in liver enzymes, ULSEPAN usage should be discontinued. (See Section 4.2)

Combined Treatment:

During combined therapy, the summaries of product characteristics of the respective medicinal products should be considered.

Gastric Malignant:

Symptomatic response to pantoprazole may mask the symptoms of gastric malignancy and delay diagnosis. In the presence of any alarm symptoms (eg, unexpected weight loss, recurrent vomiting, dysphagia, hematemesis, anemia, or melena) and in the presence or suspicion of gastric ulcer, the possibility of malignancy should be excluded.

If symptoms persist despite appropriate treatment, further investigations should be performed.

Concomitant Use with HIV Protease Inhibitors:

Co-administration of pantoprazole with HIV protease inhibitors whose absorption is dependent on acidic intragastric pH, such as atazanavir, is not recommended because of their significant reduction in bioavailability (See Section 4.5).

Influence on Vitamin B12 Absorption:

In patients with Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions requiring long-term treatment; pantoprazole may reduce the absorption of vitamin B12 (cyanocobalamin) as all acid-blocker medicines, due to hypochlorhydria or achlorhydria. This case should be considered in patients with reduced B12 body stores or have risk factors for reduced absorption on long-term therapy or in case of observation of respective clinical symptoms.

Long Term Treatment:

In long-term treatment, especially when exceeding a treatment period of one year, patients should be monitored regularly.

Bone Fracture:

Published various observations have been thought that proton pump inhibitor (PPI) treatment may associated with the increase the risk of hip, wrist and spine fracture depending osteophorosis.

Fracture risk has been increased in patients who are taken in high dose, which are described as multiple daily doses and long-term PPI treatment (1 year or more). Patients should receive the adequate lowest dose and shortest-term PPI treatment for the condition that they are treated.

Observational studies reveal that PPI's can increase the overall fracture risk by 10-40%. Some of this increase may be related to other risk factors. Patients at risk of osteoporosis should be treated in accordance with current treatment guidelines and should receive adequate amounts of vitamin D and calcium.

Hypomagnesaemia:

Rarely symptomatic and asymptomatic hypomagnesaemia has been reported in patients treated with PPIs for at least three months, and in most cases after one year of treatment. Severe adverse cases include fatigue, tetanus, delirium, dizziness, convulsion, ventricular arrhythmias and seizures. In most patients, hypomagnesaemia treatment requires magnesium replacement and discontinuation of the PPI treatment.

For patients expected to recieve prolonged treatment or take PPIs with drugs like digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics); health care professionals may follow magnesium levels before and after of starting PPI treatment and periodically.

Interactions with Examinations Performed for Neuroendocrine Tumors:

Serum cromogranin A (CgA) level increases as secondarly drug-induced decrease in gastric acid level. Increased (CgA) level may cause wrong positive results in performed diagnosis observations for neuroendocrine tumors. Operators should discontinue to PPI treatment

temporarily for at least 5 days before they evaluate CgA level and if initial CgA level is high, test should be repeated 14 days later after the discontinuation of PPI therapy. If serial tests are performed (e.g.: for monitorization), tests should be performed the same laboratory since reference intervals between tests may change.

Using with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

The use of ULSEPAN for the prevention of gastroduodenal ulcer induced by non-selective NSAIDs should be limited to patients who need continuous NSAID therapy and have an increased risk for developing gastrointestinal complications. The increased risk should be evaluated according to individual risk factors, e.g. high age (over 65 years of age), history of gastric or duodenal ulcer or history of upper gastrointestinal bleeding.

Gastrointestinal Infections Caused by Bacteria:

Treatment with proton pump inhibitors (PPIs) may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or *C. fiddicile.*

Subacute Cutaneous Lupus Erythematosus

Proton pump inhibitors have been associated with very rare cases of subacute cutaneous lupus erythematosus. In the event of lesions occurring and accompanied by arthralgia, particularly in sun-exposed areas of the skin, the patient should seek immediate medical attention and the healthcare professional should consider discontinuing ULSEPAN therapy. The development of subacute cutaneous lupus erythematosus after a previous proton pump inhibitor treatment increases the risk of the same situation with other proton pump inhibitors.

Laboratory Tests:

An increased Chromogranin A (CgA) level may affect the investigations for neuroendocrine tumors. To avoid this, Ulsepan treatment should be stopped at least 5 days before CgA measurements (See Section 5.1). If CgA and gastrin levels have not returned to the reference

range after the first measurement, measurements should be repeated 14 days after discontinuation of proton pump inhibitor therapy.

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Alcohol consumption should be avoided during treatment as alcohol may cause irritation of the gastric mucosa.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

Medicinal Products with Ph Dependent Absorption Pharmacokinetics

Because of inhibition of severe and long-term gastric acid secretion, ULSEPAN may affect the absorption of some azole anti-fungals such as ketoconazole, itraconazole, posaconazole and other medicines such as erlotinib, whe ULSEPAN is an important determinant in the oral utilization of gastric pH.

HIV Protease Inhibitor

Concomitant use of pantoprazole with HIV protease inhibitors whose absorption is dependent on acidic intragastric pH, such as atazanavir, is not recommended due to the significant reduction in their bioavailability (See Section 4.4).

If the combination of HIV protease inhibitors with a proton pump inhibitor cannot be avoided, close clinical monitoring (eg, viral load) is recommended. A dose of 20 mg of pantoprazole per day should not be exceeded. The dosage of HIV protease inhibitors may need to be adjusted.

Coumarin Anticoagulants (Phenprocoumon or Warfarin):

Although no interaction is observed during concomitant administration with phenprocoumon or warfarin in clinical pharmacokinetic studies. However, a few isolated cases of changes in International Normalised Ratio (INR) have been reported among patients receiving PPIs concomitantly with phenprocoumon or warfarin in the post-marketing period. Patients treated with pantoprazole and warfarin or phenprocoumon should be monitored for increases in INR and prothrombin time.

Methotrexate:

Concomitant use of high-dose methotrexate (e.g. 300 mg) and a proton pump inhibitor has been reported to increase methotrexate levels in some patients. Therefore, temporary discontinuation of pantoprazole may need to be considered when using high-dose methotrexate, for example for cancer and psoriasis.

Other Interactions Studies:

Pantoprazole is extensively metabolised 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.

Interaction studies with drugs also metabolised with these pathways like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl stradiol that are metabolized by the same enzyme system do not indicate clinically relevant interactions.

The interaction of pantoprazole with other medicinal products or compounds metabolized using the same enzyme system cannot be excluded.

Results from a range of interaction studies demonstrate that pantoprazole does not effect 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 affect absorption of digoxin related to p-glycoprotein.

There were no interactions observed with concomitantly administered with antacids.

Interaction studies have also been performed administering pantoprazole concomitantly with the antibiotics like clarithromycin, metronidazole, and amoxicillin. No clinically significant interactions were observed.

Medicinal products that inhibit or induce CYP2C19: CYP2C19 inhibitors such as fluvoxamine may increase systemic exposure to pantoprazole. In patients treated with CYP2C19 inhibitors, such as fluvoxamine, or in those with hepatic impairment, a reduction in the dose of pantoprazole may be considered in the long-term use of high doses of pantoprazole.

Enzyme inducers that affect CYP2C19 and CYP3A4, such as rifampicin and St. John's wort (Hypericum perforatum), may decrease the plasma concentrations of PPIs metabolized by these enzyme systems.

Additional information about special population:

No interaction studies have been performed about special population.

4.6. Pregnancy and Lactation

General advice:

Pregnancy category: B

Women of childbearing potential/Birth Control (Contraception):

It has not been observed clinically significiant interaction in specific tests performed with an oral contraceptive containing levonorgestrel and ethynyl estradiol (See Section 4.5).

Pregnancy period

Data from a limited number of pregnancy exposure cases (between 300-1000 pregnancy results) do not indicate that Pantoprazole has adverse effects on pregnancy or on the health of the fetus/newborn child (causing malformations or having foeto/neonatal toxicity). No significant epidemiological data have been obtained to date. Animal studies have shown reproductive toxicity (see Section 5.3).

The potential risk for humans is unknown.

As a precaution, the use of ULSEPAN should be avoided during pregnancy.

Lactation period

Animal studies have shown excretion of pantoprazole in breast milk. It has been reported that pantoprazole is excreted also into human milk. A risk to newborns/infants cannot be excluded. Therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with ULSEPAN should be made taking into account the benefit of breast-feeding to the child and the benefit of ULSEPAN therapy to women.

Reproductive ability/Fertility

There is no evidence of impaired fertility in animal studies following administration of pantoprazole (See Section 5.3).

4.7. Effects on Ability to Drive and use Machines

Pantoprazole has no or negligible influence on the ability to drive and use machines.
Adverse drug reactions such as dizziness and visual disturbances may occur (See Section 4.8).
In case of observation of these adverse effects, patients should not drive or operate machines.

4.8. Undesirable Effects

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

Frequency degrees of undesirable effects listed below according to system organ class have been described as following:

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). Adverse reactions in each frequency group are presented in order of decreasing seriousness.

Table 1. Adverse reactions with the use of pantoprazole in clinical studies and post-marketing experience

Frequency / Organ system	Common (≥1/100 <1/10)	Uncommon (≥1/1.000 <1/100)	Rare (≥1/10,000 <1/1,000)	Very rare (<1/10,000 İncluding isolated reports)	Not known
Blood and lymphatic system disorders			Agranulocytosis	Thrombocytopenia; Leukopenia Pancytopenia	

Immune system disorders			Hypersensitivity (including anaphylactic shock and anaphlactic reactions)		
Metabolism and nutrition disorders			Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia, hypomagnesaemia (See Section 4.4.) Hypocalcemia [(1)]; Hypokalemia
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		Dizziness; Headache	Tasting disorders		Paresthesia
Eye disorders			Eye disorders (blurred vision)		
Gastrointestinal Disorders	Fundic gland polyps (benign)	Nausea/vomiting; Abdominal pain and bloating; Constipation; Dry mouth; Abdominal strain and discomfort; Diarrhoea			
Hepatobiliary disorders		Liver enzymes increased (transaminases, γ-GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and subcutaneous tissue disorders		Rash, exanthema and skin eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity, Subacute cutaneous lupus erythematosus (see section 4.4)

Musculoskeletal and connective tissue disorders		Fracture of the hip, wrist or spine (see section 4.4)	Athralgia; Myalgia		Muscle spasm [2]
Renal and urinary disorders					Interstitial nephritis (with the possibility of progression to renal failure)
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions		Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

[1] Hypocalcemia in association with hypomagnesemia

[2] Muscle spasm as a result of electrolyte disturbances

4.9. Overdose and Treatment

There are no known symptoms of overdose in people.

It was applied up to 240 mg intravenously doses within 2 minutes and it was well tolerated.

As pantoprazole is extensively protein bound, it is not readily dialysable.

In the case of overdose with clinical signs of intoxication, except symptomatic and supportive treatment, no specific therapeutic application is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.l. 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 blockade of the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic environment in the parietal cells and 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 within two weeks. As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases 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, it can inhibit hydrochloric acid secretion independently of the stimulation by other substances (acetylcholine, histamine, gastrin). Pantoprazole has the same effect whether administered orally or intravenously.

Pharmacodynamic effects:

The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the upper limit of normal. 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 (See Section 5.3) have not been observed in humans.

During treatment with antisecretory medicinal products, serum gastrin levels are elevated in response to decreased gastric acid release. At the same time, CgA increases due to decreased gastric acidity. Elevated CgA levels may cause false results in diagnostic studies for neuroendocrine tumors.

According to some valid published evidence, treatment with proton pump inhibitors should be interrupted 5-14 days before CgA level measurement. The reason for this application is to allow CgA levels, which have increased due to PPI treatment, to decrease to reference values.

Decreased gastric acidity for any reason, including proton pump inhibitors, results in an increase in the number of bacteria normally present in the gastrointestinal tract.

Treatment with proton pump inhibitors may lead to a slightly increased risk of gastrointestinal infections like *Clostridum difficile* caused by bacteria such as *Salmonella* and *Campylobacter*.

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

5.2 Pharmacokinetic Properties

General properties

Absorption:

Pantoprazole is rapidly absorbed and the maximal plasma level is achieved even after one single 40 mg oral dose. After average 2.5 hours from administration, the serum concentrations of about 2 – 3 µg/ml are achieved and these values remain constant after multiple administration.

Pharmacokinetics do not vary after single or repeated administration.

Absolute bioavailability of tablet is about 77%. Concomitant intake of food had no influence on Area Under the Curve AUC, maximum serum concentrations and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Distribution:

Binding of pantoprazole to serum protein is about 98%. Volume of distribution is about 0.15 l/kg.

Biotransformation:

Pantoprazole is almost exclusively metabolised in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathways include oxidation by CYP3A4.

Elimination:

The terminal half-life is about one hour and the clearance is about 0.1 L/h/kg. A few cases of delayed elimination have been observed. Due to the specific binding of pantoprazole to the proton pumps of parietal cells, the elimination half-life is not proportional to longer durations of action (inhibition of acid secretion).

Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole; the rest is excreted with the faeces. The main metabolite in both serum and urine is desmethylpantoprazole, which is sulfate-conjugated. The half-life of the main metabolite (approximately 1.5 hours) is not much longer than that of pantoprazole.

Linearity/Non-linear case:

Pharmacokinetics of pantoprazole do not vary after single or repeated dose. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

Characteristic properties in patients

Poor metabolizers:

Approximately 3 % of the European population lack a functional CYP2C19 enzyme and they are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4 enzyme. 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 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 pantoprazole.

Renal failure:

No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialysed. Although the main metabolite has a moderately delayed half-life (two to three hours), excretion is still rapid and thus accumulation does not occur.

Liver failure:

Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between seven and nine hours and the AUC values increased by a factor of five to seven, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.

Pediatric population:

Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5 to 16 years AUC and C_{max} were in the range of corresponding values in adults. Following administration of single intravenous doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 to 16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

Geriatric population:

A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.

5.3 Preclinical Safety Data

Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In the two-year carcinogenicity tests 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 allows the conclusion 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 tumours was observed in rats and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.

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 a peri-postnatal rat reproduction study designed to assess bone growth, signs of offspring toxicity (mortality, low mean body weight, low mean body weight gain and reduced bone development) were observed at exposures (C_{max}) of approximately 2 times the human clinical exposure. Bone parameters at the end of the recovery phase were similar between the groups, and body weights also tended to be reversible after the drug-free recovery period. Increased mortality has been reported only in weaned rat pups (up to 21 days) and is estimated to correspond to

infants up to 2 years of age. The relevance of this finding to the pediatric population is uncertain. A previous peri-postnatal study in rats at lower doses of 3 mg/kg showed no adverse effects compared to the lower dose of 5 mg/kg.

Investigations revealed no evidence of impaired fertility or teratogenic effects.

Penetration 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

Core

Mannitol

Calcium carbonate

Crospovidone

Copovidone

Sucrose stearate

Calcium stearate

Coating

Opadry® White Y-1-7027

-Hypromellose

-Titanium dioxide (E171)

-Triacetine

Acryl-EZE® Yellow (93O92157)

-Methacrylic acid copolymer

-Talc

-Titanium dioxide (E171)

-Triethyl citrate

-Silica

-Sodyum bicarbonate

-Yellow iron oxide (E172)

-Sodium lauryl sulphate

6.2. Incompatibilities

There are no known incompabilities.

6.3. Shelf life

24 months

6.4. Special Precautions for Storage

Store below 30ºC at room temperature.

6.5. Nature and Contents of Package

In box, in Polyamide/Alu/PVC-Alu foil blister package (14 and 28 tablets).

6.6. Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

World Medicine İlaç San. ve Tic. A.Ş.
Güneşli/Bağcılar

8. MARKETING AUTHORIZATION NUMBER(S)

09404/10336/NMR/2022

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization:

Dec 31, 2023

10. DATE OF REVISION OF THE SPC