Summary of Product Characteristics (SPC)

1. Name of the medicinal product

PILOT-D TABLETS

2. Qualitative and Quantitative Composition

Label Claim:

Each enteric coated tablet Contains:

Pantoprazole Sodium Sesquihydrate eq. to Pantoprazole BP…… 20 mg

Domperidone BP…..10 mg

Excipient ..... Q.S.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Dosage Form: Tablet

Description: Red colored, round shape, biconvex, enteric-coated tablet.

4. Clinical Particulars

4.1 Therapeutic indications

Domperidone and Pantoprazole is a combination of two medicines: Domperidone and Pantoprazole. This combination is used to treat acidity, heartburn or Gastroesophageal Reflux Disease (GERD), a condition where the acid in the stomach flows back up into the food pipe (esophagus).

- Gastro-esophageal reflux disease(GERD)
- Erosive esophagitis •

Gastric and duodenal ulcers

- The relief of the symptoms of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents.

4.2 Posology and method of administration

Posology

One tablet to be taken 1-3 times a day. The tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

Pediatric

PILOT-D TABLETS are not recommended in children below 12 years of age.

Hepatic impairment

A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment.

Domperidone is contraindicated in moderate or severe hepatic impairment. Hence, a PILOT-D TABLETS is contraindicated in patients with moderate or severe hepatic impairment.

Renal impairment

In subjects with renal insufficiency (creatinine clearance< 30 ml/min/1.73m2) the elimination half-life of domperidone was increased from 7.4 to 20.8 hours. Since very little unchanged drug (approx. 1%) is excreted via the kidneys, it is unlikely that the dose of a single administration needs to be adjusted in patients with renal insufficiency. However, on repeated administration, the dosing frequency of PILOT-D TABLETS should be reduced to once or twice daily depending on severity of the impairment.

If you take more PILOT-D TABLETS than you should consult your doctor or pharmacist. There are no known symptoms of overdose.

If you forget to take PILOT-D TABLETS do not take a double dose to make up for a forgotten dose. Take your next, normal dose at the usual time.

If you stop taking PILOT-D TABLETS do not stop taking these tablets without first talking to your doctor or pharmacist

4.3 Contraindications

PILOT-D TABLETS are contraindicated in the following:

- In patients with a known hypersensitivity to pantoprazole or domperidone or any other inactive ingredients of the tablets.
- Prolactin-releasing pituitary tumour (prolactinoma).

- When stimulation of the gastric motility could be harmful: gastrointestinal haemorrhage, mechanical obstruction or perforation.
- Hepatic and/or renal impairment.

PANTOPRAZOLE: Pantoprazole is contraindicated in patients with known hypersensitivity to any component of the formulation or any substituted benzimidazole. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, acute kidney injury, and urticaria.

DOMPERIDONE: Domperidone is contraindicated in the following situations: Known hypersensitivity to domperidone or any of the excipients. Prolactin-releasing pituitary tumour (prolactinoma.) Domperidone should not be used when stimulation of gastric motility could be harmful: gastrointestinal haemorrhage, mechanical obstruction or perforation

4.4 Special warnings and precautions for use

PANTOPRAZOLE

Concurrent Gastric Malignancy: Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy.

Atrophic Gastritis: Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with pantoprazole, particularly in patients who were Helicobacter pylori positive.

Cyanocobalamin (Vitamin B12) Deficiency: Generally, daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (Vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acidsuppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

Bon Fracture: Several published observational studies suggest that 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 longterm 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 osteoporosisrelated fractures should be managed according to established treatment guidelines.

Hypomagnesaemia: Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least 3 months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias and seizures. In most patients, treatment of hypomagnesaemia 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), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Tumourigenicity: Due to the chronic nature of GERD, there may be a potential for prolonged administration of pantoprazole. In long-term rodent studies, pantoprazole was carcinogenic and caused rare types of gastrointestinal tumours. The relevance of these findings to tumour development in humans is unknown.

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: Pantoprazole, like all PPIs, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as Salmonella and Campylobacter.

DOMPERIDONE

Patients who find they have post-prandial symptoms that persist, and are having to take domperidone continuously for more than 2 weeks should consult their doctor. Patients who find that their nausea and vomiting persists for more than 48 hours should consult their doctor. Domperidone is not recommended for the treatment of motion sickness. Domperidone is also not recommended for use in patients with underlying cardiac disease without medical supervision. These tablets contain lactose and may be unsuitable for patients with lactose intolerance, galactosaemia or glucose/galactose malabsorption.

Use with Potent CYP3A4 Inhibitors: Co-administration with oral ketoconazole, erythromycin or other potent CYP3A4 inhibitors that prolong the QTc interval should be avoided.

Cardiac Effects: Some epidemiological studies showed that domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. The risk may be higher in patients older than 60 years and at daily doses of more than 30 mg. Domperidone should be used at the lowest effective dose in adults and children. Use of domperidone and other drugs which prolong QTc intervals requires that caution be exercised in patients who have existing prolongation of cardiac conduction intervals, particularly the QTc, and in patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of atazanavir or nelfinavir with proton pump inhibitors is not recommended. Coadministration of atazanavir or nelfinavir with proton pump inhibitors is expected to substantially decrease atazanavir or nelfinavir plasma concentrations and may result in a loss of therapeutic effect and development of drug resistance.

Coumarin Anticoagulants: There have been postmarketing reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including Pantoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly should be monitored for increases in INR and prothrombin time.

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

Drugs for Which Gastric pH can Affect Bioavailability: Due to its effects on gastric acid secretion, pantoprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Like with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, ampicillin esters, atazanavir, iron salts, erlotinib, and mycophenolate mofetil (MMF) can decrease. Co-administration of pantoprazole in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not

been established in transplant patients receiving pantoprazole and MMF. Use pantoprazole with caution in transplant patients receiving MMF.

False Positive Urine Tests for THC: There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving proton pump inhibitors. An alternative confirmatory method should be considered to verify positive results.

Methotrexate: Concomitant administration of PPIs and methotrexate 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 reported.

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

Drugs for Which Gastric pH can Affect Bioavailability: Pantoprazole causes long-lasting inhibition of gastric acid secretion. Therefore, pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

DOMPERIDONE: The main metabolic pathway of domperidone is through CYP3A4. In vitro data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone. In vivo interaction studies with ketoconazole revealed a marked inhibition of domperidone's CYP3A4 mediated first pass metabolism by ketoconazole. A pharmacokinetic study has demonstrated that the AUC and the peak plasma concentration of domperidone is increased by a factor of 3 when oral ketoconazole is administered concomitantly (at steady state). A slight QT prolonging effect (mean less than 10msec) of this combination was detected, which was greater than the one seen with ketoconazole alone. A QT prolonging effect could not be detected when domperidone was given alone in patients with no comorbidity, even at high oral doses (up to 160mg/day). The results of this interaction study should be taken into account when prescribing domperidone concomitantly with strong CYP3A4 inhibitors: for example: ketoconazole, ritonavir and erythromycin.

4.6 Fertility, pregnancy and lactation

Pregnancy

PANTOPRAZOLE: Pregnancy Reproduction studies have been reported in rats at oral doses up to 88 times the recommended human dose and in rabbits at oral doses up to 16 times the recommended human dose and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Lactation Pantoprazole and its metabolites are excreted in the milk of rats. Pantoprazole excretion in human milk has been detected in a study of a single nursing mother after a single 40 mg oral dose. The clinical relevance of this finding is not known. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity reported for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

DOMPERIDONE: Pregnancy There are limited post-marketing data on the use of domperidone in pregnant women. A study in rats has shown reproductive toxicity at a high, maternally toxic dose. The potential risk for humans is unknown. Therefore, domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit. Lactation The drug is excreted in breast milk of lactating rats (mostly as metabolites: peak concentration of 40 and 800ng/ml after oral and i.v administration of 2.5mg/kg respectively). Domperidone concentrations in breast milk of lactating women are 10 to 50% of the corresponding plasma concentrations and expected not to exceed 10ng/ml. The total amount of domperidone excreted in human breast milk is expected to be less than 7micrograms per day at the highest recommended dosing regimen. It is not known whether this is harmful to the newborn. Therefore breastfeeding is not recommended for mothers who are taking domperidone.

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. If affected, patients should not drive

or operate machines. Domperidone has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

PANTOPRAZOLE

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adults

Safety in nine randomized comparative clinical trials in patients with GERD included 1,473 patients on oral PANTOPRAZOLE (20 mg or 40 mg), 299 patients on an H2-receptor antagonist, 46 patients on another proton pump inhibitor, and 82 patients on placebo. The most frequently occurring adverse reactions are listed in Table. Adverse Reactions Reported in Clinical Trials of Adult Patients with GERD at a Frequency of > 2%

Adverse Reactions Reported in Clinical Trials of Adult Patients with GERD at a Frequency of > 2%			
	Pantoprazole (n = 1,473) %	**Comparators (n = 345) %**	**Placebo (n = 82) %**
Headache	12.2	12.8	8.5
Diarrhea	8.8	9.6	4.9
Nausea	7	5.2	9.8
Abdominal pain	6.2	4.1	6.1
Vomiting	4.3	3.5	2.4
Flatulence	3.9	2.9	3.7
Dizziness	3	2.9	1.2
Arthralgia	2.8	1.4	1.2

Additional adverse reactions that were reported for pantoprazole in clinical trials with a frequency of ≤ 2% are listed below by body system:

Body as a Whole: allergic reaction, pyrexia, photosensitivity reaction, facial edema
Gastrointestinal: constipation, dry mouth, hepatitis
Hematologic: leukopenia, thrombocytopenia
Metabolic/Nutritional: elevated CK (creatine kinase), generalized edema, elevated triglycerides, liver enzymes elevated
Musculoskeletal: myalgia Nervous: depression, vertigo Skin and Appendages: urticaria, rash, pruritus
Special Senses: blurred vision.

Pediatric Patients: Safety of pantoprazole in the treatment of Erosive Esophagitis (EE) associated with GERD was evaluated in pediatric patient's ages 1 year through 16 years in three clinical trials. Safety trials involved pediatric patients with EE; however, as EE is uncommon in the pediatric population, 249 pediatric patients with endoscopically-proven or symptomatic GERD were also evaluated. All adult adverse reactions to pantoprazole are considered relevant to pediatric patients. In patient's ages 1 year through 16 years, the most commonly reported (> 4%) adverse reactions include: URI, headache, fever, diarrhea, and vomiting, rash, and abdominal pain.

For safety information in patients less than 1 year of age see Use in Specific Population.

Additional adverse reactions that were reported for pantoprazole in pediatric patients in clinical trials with a frequency of ≤ 4% are listed below by body system.

Body as a Whole: allergic reaction, facial edema.
Gastrointestinal: constipation, flatulence, nausea.
Metabolic/Nutritional: elevated triglycerides elevated liver enzymes, elevated CK (creatine kinase).
Musculoskeletal: arthralgia, myalgia Nervous: dizziness, vertigo
Skin and Appendages: urticarial

The following adverse reactions seen in adults in clinical trials were not reported in pediatric patients in clinical trials, but are considered relevant to pediatric patients: photosensitivity reaction, dry mouth, hepatitis, thrombocytopenia, generalized edema, depression, pruritus, leukopenia, and blurred vision.

Zollinger-Ellison Syndrome: In clinical studies of Zollinger-Ellison Syndrome, adverse reactions reported in 35 patients taking pantoprazole 80 mg/day to 240 mg/day for up to 2 years were similar to those reported in adult patients with GERD.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of pantoprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These adverse reactions are listed below by body system:

General Disorders and Administration Conditions: asthenia, fatigue, malaise

Hematologic: pancytopenia, agranulocytosis

Hepatobiliary Disorders: hepatocellular damage leading to jaundice and hepatic failure Immune System Disorders: anaphylaxis (including anaphylactic shock) Infections and Infestations: Clostridium difficile associated diarrhea Investigations: weight changes

Metabolism and Nutritional Disorders: hyponatremia, hypomagnesemia

Musculoskeletal Disorders: rhabdomyolysis, bone fracture

Nervous: ageusia, dysgeusia

Psychiatric Disorders: hallucination, confusion, insomnia, somnolence

Renal and Urinary Disorders: interstitial nephritis, acute kidney injury

Skin and Subcutaneous Tissue Disorders: severe dermatologic reactions (some fatal), including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal), and angioedema (Quincke's edema)

DOMPERIDONE

Immune System Disorder: Very rare; Allergic reaction

Endocrine disorder: Rare; increased prolactin levels

Nervous system disorders: Very rare; extra pyramidal side effects.

Gastro-intestinal disorders: Rare gastro-intestinal disorders including very rare transient intestinal cramps

Skin and subcutaneous tissue disorders: Very rare; urticaria

Reproductive system and breast disorders: Rare; galactorrhoea, gynaecomastia, amenorrhoea

As the hypophysis is outside the blood brain barrier, domperidone may cause an increase in prolactin levels. In rare cases this hyperprolactinaemia may lead to neuroendrocrinological side effects such as galactorrhoea, gynaecomastia and amenorrhoea. Extrapyramidal side effects are exceptional in adults. These side effects reverse spontaneously and completely as soon as treatment is stopped.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after Authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

4.9 Overdose

PANTOPRAZOLE

Experience in patients taking very high doses of pantoprazole (> 240 mg) is limited. Spontaneous post-marketing reports of overdose are generally within the known safety profile of pantoprazole. Pantoprazole is not removed by hemodialysis. In case of overdosage, treatment should be symptomatic and supportive. Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg, and 887 mg/kg were lethal to mice, rats, and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

DOMPERIDONE

Symptoms: Symptoms of overdosage may include drowsiness, disorientation and extrapyramidal reactions, especially in children.

Treatment: There is no specific antidote to domperidone, but in the event of overdose, gastric lavage as well as the administration of activated charcoal, may be useful. Close medical supervision and supportive therapy is recommended. Anticholinergic, anti-parkinson drugs may be helpful in controlling extrapyramidal reactions.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antacid.

ATC code: A02BC02 & A03FA03

PANTOPRAZOLE: Mechanism of action: Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the H+/K+ -ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. It has been reported that the binding to the H+/K+ -ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).

DOMPERIDONE: Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood brain barrier. In domperidone users, especially in adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors. Studies in man have shown oral domperidone to increase lower oesophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

5.2 Pharmacokinetic properties

PANTOPRAZOLE

Pantoprazole is prepared as enteric-coated tablets so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (Cmax) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate, and its pharmacokinetics are unaltered with multiple daily dosing. Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially, with a terminal elimination half-life of approximately one hour. In extensive metabolizers with normal liver function receiving an oral dose of the enteric

coated 40 mg pantoprazole tablet, the peak concentration (Cmax) is 2.5 μg/mL; the time to reach the peak concentration (tmax) is 2.5 h, and the mean total area under the plasma concentration versus time curve (AUC) is 4.8 μg•h/mL (range 1.4 to 13.3 μg*h/mL). A single oral dose of pantoprazole, 40 mg, was reported to be bioequivalent when administered to healthy subjects (N = 22) as granules sprinkled over a teaspoonful of applesauce, as granules mixed with apple juice, or mixed with apple juice followed by administration through a nasogastric tube. The plasma pharmacokinetic parameters from a crossover study in healthy subjects are summarized in Table as shown below:

Pharmacokinetic Parameters	**Granulesin Appleasauce**	**Granuelesin Apple Juice**	**Granuelesin Nasogastric Tube**
AUC(μg*hr/ml)	4.0±1.5	4.0±1.5	4.0±1.7
Cmax (μg*/ml)	2.0±0.7	1.9±0.5	2.2±0.7
Tmax (hr)a	2.0	2.5	2.0
a Median Values are reported for Tmax			

Absorption: After administration of a single or multiple oral 40 mg doses of Pantoprazole, the peak plasma concentration of pantoprazole was achieved in approximately 2.5 hours, and Cmax was 2.5 μg/mL. Pantoprazole undergoes little first-pass metabolism, resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids. Administration of Pantoprazole Tablets with food may delay its absorption up to 2 hours or longer; however, the Cmax and the extent of pantoprazole absorption (AUC) are not altered. Thus, Pantoprazole may be taken without regard to timing of meals.

Distribution: The apparent volume of distribution of pantoprazole is approximately 11.0-23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin. Metabolism: Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity.

Elimination: After a single oral or intravenous dose of 14C-labeled pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine, with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

Geriatric: Only slight to moderate increases in pantoprazole AUC (43%) and Cmax (26%) were found in elderly volunteers (64 to 76 years of age) after repeated oral administration, compared with younger subjects. No dosage adjustment is recommended based on age.

Pediatric: The pharmacokinetics of pantoprazole was reported in children less than 16 years of age in four randomized, open-label clinical trials in pediatric patients with presumed/proven GERD. Pantoprazole delayed-Release tablets were studied in children older than 5 years. In a population PK analysis, total clearance increased with increasing bodyweight in a nonlinear fashion. The total clearance also increased with increasing age only in children under 3 years of age.

Children and Adolescents 6 through 16 Years of Age: The pharmacokinetics of Pantoprazole Tablets was reported in children ages 6 through 16 years with a clinical diagnosis of GERD. The PK parameters following a single oral dose of 20 mg or 40 mg of Pantoprazole tablets in children ages 6 through 16 years were highly variable (%CV ranges 40 to 80%). The geometric mean AUC estimated from population PK analysis after a 40 mg Pantoprazole tablet in pediatric patients was about 39% and 10% higher respectively in 6 to 11 and 12 to 16 year-old children, compared to that of adults.

PK parameters in childrean and adolescents 6 through 16 years with GERD receiving pantoprazole 40mg.

	6-11 Years (n=12)	**12-16 Years(n=11)**
Cmax (µg/ml)[a]	1.8	1.8
tmax (h)[b]	2.0	2.0
AUC(µg*h/ml)[2]	6.9	5.5
CL/F(L/h)[b]	6.6	6.8

a Geometric mean Values, b Median Values

Gender: There is a modest increase in pantoprazole AUC and Cmax in women compared to men. However, weight-normalized clearance values are similar in women and men. No dosage adjustment is recommended based on gender. In pediatric patients ages 1 through 16 years there were no clinically relevant effects of gender on clearance of pantoprazole, as shown by population pharmacokinetic analysis.

Renal Impairment: In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Hepatic Impairment: In patients with mild to severe hepatic impairment (Child-Pugh A to C cirrhosis), maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in CYP2C19 poor metabolizers, where no dosage adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once-daily, multiple- dose administration. No dosage adjustment is needed in patients with mild to severe hepatic impairment. Doses higher than 40 mg/day have not been reported in hepatically impaired patients.

DOMPERIDONE

Domperidone is extensive first-pass metabolism in the gut wall and liver. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. Oral domperidone does not appear to accumulate or induce its own metabolism. Domperidone is 91-93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue istribution, but low brain concentration. Small amounts of drug cross the placenta in rats. Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation in vitro metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone whereas CYP3A4, CYP1A2 AND CYP2E1 are involved in domperidone aromatic hydroxylation.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for 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 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 development, signs of offspring toxicity (mortality, lower mean body weight, lower mean body weight gain and reduced bone growth) were observed at exposures (C_{max}) approximately 2x the human clinical exposure. By the end of the recovery phase, bone parameters were similar across groups and body weights were also trending toward reversibility after a drug-free recovery period. The increased mortality has only been reported in pre-weaning rat pups (up to 21 days age) which is estimated to correspond to infants up to the age of 2 years old. The relevance of this finding to the paediatric population is unclear. A previous peri-postnatal study in rats at slightly lower doses found no adverse effects at 3 mg/kg compared with a low dose of 5 mg/kg in this study. 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

Starch

Di calcium phosphate,

Iso Propyl Alcohol

P.V.P.K-30

Sodium benzoate

Talcum

Magnesium stearate

Sodium starch Glycolate

Methylene Di Chloride

Color powder

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Storage Store in a cool dry place, Protect from light.

6.5 Nature and contents of container

3 X 10 Tablet

7. Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

NATIONAL PHARMACY LTD,

Colchester Park,

P.O Box 17843 - 00500

Nairobi, Kenya.

Manufacturer:

BRUSSELS LABORATORIES PVT. LTD.

33. Changodar Ind. Estate. Sarkhej-Bavla Road,

Changodar, Ahmedabad-382210, Gujarat, India.

8. Marketing Authorization Number:

CTD1600

9. Date of first Authorization /renewal of the authorization:

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10. Date of revision of text:

July 2024

11. DOSIMETRY (IF APPLICABLE)

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12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE):

N/A