For the use of registered medicinal practitioners/laboratory only

(Pantoprazole Enteric Coated and Domperidone Sustained Release Capsules)
PAN-D

1. Name of the medicinal product
PAN-D
2. Qualitative and quantitative composition
Each capsule contains:
Pantoprazole Sodium I. P. equivalent to Pantoprazole 40 mg
(As enteric coated pellets)
Domperidone Maleate I.P. equivalent to Domperidone 30 mg
(As sustained release pellets)
3. Pharmaceutical form
Capsules
4. Clinical particulars
4.1 Therapeutic indications
Combination of pantoprazole and domperidone is indicated for the treatment of Gastroesophageal reflux disease (GERD).
4.2 Posology and method of administration
One capsule once daily preferably before meal.
4.3 Contraindications
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 reported occasionally in gastric corpus biopsies from patients treated long-term with Pantoprazole, particularly in patients who were H. pylori positive.
Acute Interstitial Nephritis, acute kidney injury
Acute interstitial nephritis, acute kidney injury has been observed in patients taking PPIs including pantoprazole. Acute interstitial nephritis, acute kidney injury may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue pantoprazole if acute interstitial nephritis, acute kidney injury develops.
Cyanocobalamin (Vitamin B-12) 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 B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid- suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are reported.

***Clostridium difficile* associated diarrhea**

Published observational studies suggest that PPI therapy like pantoprazole may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Bone Fracture

Several published observational studies reported 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.

Hypomagnesemia

Hypomagnesemia, 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 adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia 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 hypomagnesemia (e.g., diuretics), health care professionals.

Tumorigenicity

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

Interference with Urine Screen for THC

See Drug Interactions section

Concomitant use of Pantoprazole with Methotrexate

Literature reported 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.

Pediatric Use

The safety and effectiveness of pantoprazoe for short-term treatment (up to eight weeks) of erosive esophagitis (EE) associated with GERD have been reported in pediatric patients 1 year through 16 years of age. Effectiveness for EE has not been demonstrated in patients less than 1 year of age. In addition, for patients less than 5 years of age, there is no appropriate dosage strength in an age-appropriate formulation available. Therefore, pantoprazole is indicated for the short-term treatment of EE associated with GERD for patients 5 years and older. The safety and effectiveness of Pantoprazole for pediatric uses other than EE have not been established.

1 year through 16 years of age

Use of Pantoprazole in pediatric patients 1 year through 16 years of age for short-term treatment (up to eight weeks) of EE associated with GERD is supported by: a) extrapolation of results from adequate and well-controlled studies that supported the approval of Pantoprazole for treatment of EE associated with GERD in adults, and b) safety, effectiveness, and pharmacokinetic studies performed in pediatric

patients.

Neonates to less than one year of age

Pantoprazole was not reported to be effective in the randomized, placebo-controlled study in this age group, the use of Pantoprazole for treatment of symptomatic GERD in infants less than 1 year of age is not indicated.

Geriatric Use

In short-term reported clinical trials, erosive esophagitis healing rates in the 107 elderly patients (≥ 65 years old) treated with Pantoprazole were similar to those found in patients under the age of 65. The incidence rates of adverse reactions and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.

Gender

Erosive esophagitis healing rates in the 221 women treated with Pantoprazole Delayed- Release Tablets in US clinical trials were similar to those found in men. In the 122 women treated long-term with Pantoprazole 40 mg or 20 mg, healing was maintained at a rate similar to that in men. The incidence rates of adverse reactions were also similar for men and women.

Patients with Hepatic Impairment

Doses higher than 40 mg/day have not been studied in patients with hepatic impairment.

DOMPERIDONE

Precautions for use Use during lactation

The total amount of domperidone excreted in human breast milk is expected to be less than 7 micrograms per day at the highest recommended dosing regimen. It is not known whether this is harmful to the newborn. Therefore breast-feeding is not recommended for mothers who are taking domperidone.

Use in infants

Neurological side effects are rare. Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life the risk of neurological side effects is higher in young children. Therefore, it is recommended that the dose be determined accurately and followed strictly in children. Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

Use in liver disorders

Since domperidone is highly metabolised in the liver, domperidone should be not be used in patients with hepatic impairment

Renal insufficiency

In patients with severe renal insufficiency (serum creatinine > 6 mg/100 mL, i.e. > 0.6 mmol/L) the elimination half-life of domperidone was increased from 7.4 to 20.8 hours, but plasma drug levels were lower than in healthy volunteers. Since very little unchanged drug 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 should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced. Such patients on prolonged therapy should be reviewed regularly.

Use with ketoconazole

A slight increase of QT interval (mean less than 10msec) was reported in a drug-drug interaction study with oral ketoconazole. Even if the significance of this study is not fully clear, alternative therapeutic options should be considered if antifungal treatment is required.

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.

4.5 Interaction with other medicinal products and other forms of interaction

PANTOPRAZOLE

Interference with Antiretroviral Therapy

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).

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.

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

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

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

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: urticaria

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.

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

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 (C_{max}) 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	**Granules in Appleasauce**	**Granueles in Apple Juice**	**Granueles in Nasogastric Tube**
AUC(µg*hr/ml)	4.0±1.5	4.0±1.5	4.0±1.7
C_{max} (µg*/ml)	2.0±0.7	1.9±0.5	2.2±0.7
T_{max} (hr)[a]	2.0	2.5	2.0
a Median Values are reported for T_{max}			

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 ^{14}C-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)**
C_{max} (µg/ml)[a]	1.8	1.8

t_{max} (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.

6. Pharmaceutical particulars

6.1 Shelf life

24 Months

6.2 Special precautions for storage

Store in a cool dry place, protected from light.

6.3 Nature and contents of container

Strip

7. Marketed By

ALKEM

Alkem Laboratories Ltd.
ALKEM HOUSE,
S. B. Road, Lower Parel (West),
Mumbai - 400 013. INDIA.

8. DATE OF REVESION OF TEXT

September 2019