For the use of registered medicinal practitioners/laboratory only

PAN 20/40
(Pantoprazole Tablets)

1. Name of the medicinal product

PAN 20/40

2. Qualitative and quantitative composition

PAN 20

Each enteric coated tablet contains:

Pantoprazole sodium I.P. Equivalent to Pantoprazole 20 mg

PAN 40

Each enteric coated tablet contains:

Pantoprazole sodium I.P. Equivalent to Pantoprazole 40 mg

3. Pharmaceutical form

Enteric coated tablets

4. Clinical particulars

4.1 Therapeutic indications

For treatment of Gastric ulcer, duodenal ulcer, Zollinger-Ellison Syndrome and Gastro esophageal Reflux Disease (GERD).

4.2 Posology and method of administration

Recommended Dosing Schedule

Indication	**Dose**	**Frequency**
Short-Term Treatment of Erosive Esophagitis Associated With GERD		
Adults	40 mg	Once daily for up to 8 weeks *
Children (5 years and older) ≥ 15kg to < 40 kg	20 mg	Once daily for up to 8 week
≥ 40 kg	40 mg	
Maintenance of Healing of Erosive Esophagitis		
Adults	40mg	Once daily
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome		
Adults	40 mg	Twice daily**

*For adult patients who have not healed after 8 weeks of treatment, an additional 8- week course of Pantoprazole may be considered.

** Dosage regimens should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 240 mg daily have been administered.

Administration Instructions

It should be swallowed whole, with or without food in the stomach. If patients are unable to swallow a 40 mg tablet, two 20 mg tablets may be taken. Concomitant administration of antacids does not affect the absorption.

4.3 Contraindications

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.

4.4 Special warnings and precautions for use

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.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy, unless clearly necessary.

Breast-feeding

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

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

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.
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)

4.9 Overdose

There are no known symptoms of overdose in man.
Systemic exposure with up to 240 mg administered intravenously over 2 minutes, were well tolerated.
As pantoprazole is extensively protein bound, it is not readily dialysable.
In the case of an overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02BC02
Mechanism of action
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells.
Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H+, K+-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved within 2 weeks. As with other proton pump inhibitors and H2 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 stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given 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.
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

Pantoprazole Tablets are 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 Tablets, 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 Tablets 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.

5.3 Preclinical safety data

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

In the two-year carcinogenicity studies in rats neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and 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 tumors 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 animal reproduction studies, signs of slight fetotoxicity were observed at doses above 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 Shelf life

30 Months

6.2 Special precautions for storage

Store in a cool dry place, protected from light.

6.3 Nature and contents of container

Blister Pack

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

November 2019