1. NAME OF THE DRUG PRODUCT

Pantonex DR-40 (Pantoprazole 40mg Delayed-Release Tablets)

Strength

Each Enteric Coated Tablet Contains:
Pantoprazole Sodium Sesquihydrate EP equivalent to Pantoprazole… 40mg

Pharmaceutical/Dosage form

Enteric Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative declaration

Pantoprazole is a substituted benzimidazole, sodium 5-(difluoromethoxy)- 2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_2N_3NaO_4S$ x 1.5 H_2O, with a molecular weight of 432.4.

Quantitative declaration

Each Enteric Coated Tablet Contains:
Pantoprazole Sodium Sesquihydrate EP equivalent to Pantoprazole… 40mg

Salts and hydrates

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3. PHARMACEUTICAL FORM

“Yellow colored, oval, biconvex enteric coated tablets plain on both sides”

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pantoprazole delayed release tablets are indicated for

Short-term treatment in the healing and symptomatic relief of erosive esophagitis associated with gastroesophageal reflux disease (GERD)

Maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in patients with gastroesophageal reflux disease (GERD).

Treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)

Improvement and healing of duodenal ulcer and gastric ulcer

Long term treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome

Eradication of Helicobacter pylori, in combination with two antibiotics in patients with duodenal ulcer or gastritis.

Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment

4.2 Posology/Dosage and method of administration
Oral
Posology/Dosage

Special populations

Method of administration

4.3 Contraindications
Pantoprazole delayed release tablets are contraindicated in patients with known hypersensitivity to pantoprazole, any other ingredient in the formulation or other substituted benzimidazoles (e.g. esomeprazole, lansoprazole, omeprazole, rabeprazole). Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticarial.

4.4 Special warnings and precautions for use
Sensitivity reactions
Anaphylaxis has been reported with the use of intravenous pantoprazole sodium. Immediate medical intervention and drug discontinuance are required if anaphylaxis or other severe hypersensitivity reaction occurs.

Concurrent gastric malignancy
Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy. In the presence of any alarm symptom (e. g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment

Atrophic gastritis
Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with pantoprazole, particularly in patients who were H. 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 acid suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

Clostridium difficile associated diarrhea
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
Proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine, predominantly in older people or in the presence of other recognized risk factors. The risk of fracture increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Proton pump inhibitors may increase the overall risk of fracture by 10 – 40%. 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. They should have an adequate intake of vitamin D and calcium.

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 may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically

Tumorigenicity
Due to the chronic nature of GERD, there may be a potential for prolonged administration of pantoprazole. In experimental animals, pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these findings to tumor development in humans is unknown.

Liver impairment
In patients with severe liver impairment, particularly those on long-term use, liver enzymes should be monitored regularly during treatment with pantoprazole. In the case of a rise in liver enzymes, pantoprazole should be discontinued.

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
Decreased gastric acidity due to any means – including proton pump inhibitors – increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to a slightly increased risk of gastrointestinal infections, such as Salmonella, C. difficile and Campylobacter.

Respiratory effect
Administration of proton pump inhibitor has been associated with an increased risk of developing certain infections (e.g. community acquired pneumonia)

Co-administration with NSAIDs
The use of pantoprazole as a preventive of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. high age (>65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

Acute interstitial nephritis
Acute interstitial nephritis has been observed in patients taking PPIs including pantoprazole tablets. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue pantoprazole tablets if acute interstitial nephritis develops

Effects on 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.

Usage in pregnancy and lactation
There are 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.

Pantoprazole and its metabolites are excreted in the milk of rats. Pantoprazole excretion in human milk has been detected in 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 shown 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.

Usage in paediatrics
The safety and effectiveness of pantoprazole tablets for short-term treatment (up to eight weeks) of erosive esophagitis (EE) associated with GERD have been established 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 tablets are indicated for the short-term treatment of EE associated with GERD for patients 5 years and older. The safety and effectiveness of pantoprazole tablets for pediatric uses other than EE have not been established.

Usage in geriatrics
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.

4.5 Interaction with other drug products and other forms of interaction
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.

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.

Drugs for which gastric pH can affect bioavailability
Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with 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, itraconazole, posaconazole and other medicine as erlotinib, ampicillin esters, mycophenolate mofetil (MMF) and iron salts 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 sodium delayed-release tablets and MMF. Use pantoprazole tablets with caution in transplant patients receiving MMF.

Sucralfate
Potential delayed absorption and decreased bioavailability of proton pump inhibitor (e.g. lansoprazole, omeprazole); administer proton pump inhibitor at least 30 minutes before sucralfate.

Antacids
There was also no interaction with concomitantly administered antacids.

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

Methotrexate
Concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

Drugs that cause hypomagnesemia
Potential pharmacologic interaction (possible increased risk of hypomagnesemia). In patients receiving diuretics (i.e. loop or thiazide diuretics) or other drugs that may cause hypomagnesemia, monitoring of magnesium concentration should be considered prior to initiation of prescription proton pump inhibitor therapy and periodically thereafter.

Digoxin
Hypomagnesemia (e.g. resulting from long term use of proton pump inhibitors) sensitize the myocardium to digoxin and thus may increase the risk of digoxin induced cardiotoxic effects. In patients receiving digoxin, monitoring of magnesium concentrations should be considered prior to initiation of prescription proton pump inhibitor therapy and periodically thereafter.

Others
Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. Based on studies evaluating possible interactions of pantoprazole with other drugs, no dosage adjustment is needed with concomitant use of the following: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam (and its active metabolite, desmethyldiazepam), diclofenac, naproxen, piroxicam, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin, midazolam, clarithromycin, metronidazole, or amoxicillin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when coadministered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary.

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.

4.6 Fertility, pregnancy and lactation
There are 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.

Pantoprazole and its metabolites are excreted in the milk of rats. Pantoprazole excretion in human milk has been detected in 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 shown 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.

4.7 Effects on 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.

4.8 Undesirable effects
The adverse reactions reported with pantoprazole are listed below, ranked under the following frequency classification: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Blood and lymphatic system disorders
Rare: Agranulocytosis; Very rare: leukopenia, thrombocytopenia, pancytopenia

Eye disorders
Rare: Disturbances in vision/blurred vision

Gastrointestinal disorders
Uncommon: Diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort, flatulence

General disorders and administration site conditions
Uncommon: Asthenia, fatigue and malaise; Rare: Body temperature increased (Pyrexia), oedema peripheral; Not known: Facial edema, generalized edema

Hepato-biliary disorders
Uncommon: Liver enzymes increased (transaminases, γ-GT); Rare: Bilirubin increased; Not known: Hepatocellular injury, jaundice, hepatic failure, hepatitis

Immune system disorders
Rare: Hypersensitivity (including anaphylactic reactions and anaphylactic shock)

Infections and infestations
Not known: Clostridium difficile associated diarrhea

Investigations
Not known: Elevated creatine kinase, weight changes

Metabolic and nutritional disorders
Rare: Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes; Not known: Hyponatraemia, hypomagnesaemia, hypocalcaemia in association with hypomagnesemia, hypokalaemia.

Musculoskeletal and connective tissue disorders
Uncommon: Fracture of the hip, wrist or spine; Rare: Arthralgia, myalgia, rhabdomyolysis, bone fracture; Not known: Muscle spasm

Nervous system disorders
Uncommon: Headache, dizziness; Rare: Taste disorders, vertigo, ageusia, dysgeusia; Not known: Paraesthesia

Psychiatric disorders
Uncommon: Sleep disorders; Rare: Depression (and all aggravations); Very Rare: Disorientation (and all aggravations); Not known: Hallucination, confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence), insomnia, somnolence

Renal and urinary disorders
Not known: Interstitial nephritis (with possible progression to renal failure)

Reproductive system and breast disorders
Rare: Gynaecomastia

Skin and subcutaneous tissue disorders
Uncommon: Rash/exanthema/eruption, pruritus; Rare: Urticaria, angioedema (Quincke's edema); Not known: Severe dermatologic reactions (some fatal) including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN, some fatal), Lyell syndrome; photosensitivity

Effect on electrolytes
For mention of a fall in blood electrolytes during treatment with proton pump inhibitors including pantoprazole

4.9 Overdose
Doses up to 240 mg administered intravenously over 2 minutes were well tolerated. Experience in patients taking very high doses of pantoprazole (>240mg) is limited. Spontaneous post-marketing reports of overdose are generally within the known safety profile of pantoprazole. There are no known symptoms of overdose in man.
As pantoprazole is extensively protein bound, it is not removed by hemodialysis. In case of overdosage, treatment should be symptomatic and supportive, no specific therapeutic recommendations can be made.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
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.

Pantoprazole accumulates, in the acidic environment of the parietal cells after absorption. There it is converted into the active form, a cyclic sulphenamide, which binds to the H+, K+-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distally to the receptor level, it can inhibit gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

The binding to the (H+,K+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours.

Pantoprazole's selectivity is due to the fact that it can only exert its full effect in a strongly acidic environment (pH<3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological and thus therapeutic effect can only be achieved in the acid-secretory parietal cells. By means of a feedback mechanism, this effect is diminished at the same rate as acid secretion is inhibited.

Following oral administration, pantoprazole inhibits the pentagastrin- stimulated gastric acid secretion.

Antisecretory activity
Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Acid secretion returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion. At oral doses ranging from 20 to 120 mg, pantoprazole caused dose-related increases in median basal gastric pH. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH.

Serum gastrin effects
There was an increase in mean gastrin levels in patients treated with pantoprazole for 4 or 8 weeks. Median serum gastrin levels remained within normal limits during maintenance therapy with pantoprazole.

Following healing of gastric or duodenal ulcers with pantoprazole treatment, elevated gastrin levels return to normal by at least 3 months.

Enterochromaffin-Like (ECL) Cell effects
In experimental animals, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors may result from chronic elevation of serum gastrin concentrations. However, there were no elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day.

Other effects
No clinically relevant effects of pantoprazole on cardiovascular, respiratory, ophthalmic, or central nervous system function have been detected. Pantoprazole 40 mg given once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle- stimulating hormone, luteinizing hormone, prolactin, and growth hormone.

5.2 Pharmacokinetic properties
The drug is prepared as an enteric-coated tablet so that absorption of pantoprazole begins only after the tablet leaves the stomach.

Pantoprazole is well absorbed. It undergoes little first-pass metabolism Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing.

Administration of pantoprazole 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. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. 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.

Approximately 71% of the dose is excreted in the urine with 18% excreted in the feces through biliary excretion. There is no renal excretion of unchanged pantoprazole. Following oral administration, the serum concentration of pantoprazole declines biexponentially, with a terminal elimination half-life of approximately one hour. Because of the specific activation within the parietal cell, the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Special populations
Renal impairment
No change in pharmacokinetic parameters was seen in patients with severe renal impairment. 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, maximum pantoprazole concentrations increased only slightly. Although there is increase in serum half-life values and AUC values in hepatic-impaired patients, these increases were no greater than those observed in slow CYP2C19 metabolizers, where no dosage frequency 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 studied in hepatically-impaired patients.

5.3 Preclinical safety data
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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mannitol (Pearlitol SD 200), Sodium Carbonate (anhydrous), Soidum Starch Glycollate (Primojel), Crospovidone (Kollidone CL), Colloidal Silicon Dioxide (Aerosil 200), Calcium Stearate, HPMC-5 cps, Polyethylene Glycol (PEG 6000), Purified Water, Sodiim Hydroxide, Eudragit L 30 D 55, Opadry AMB 80W52172

6.2 Incompatibilities

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not store above 30°C. Store in dry condition. Keep out of reach of children

6.5 Nature and contents of container
Blister strip of 10 tablets. Such 3 blister strips in a printed showbox along with leaflet.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product
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7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Ipca Pharma Nig Ltd.
No, 3, Ilupeju Bye Pass.
(Olajire House)
Ilupeju Lagos.
ipcaharma@yahoo.com

8. DRUG PRODUCT MANUFACTURER

Ipca Laboratories Limited,
Plot No. 255/1, Village-Athal,
Silvassa - 396230, U.T. of Dadra and
Nagar Haveli and Daman and Diu, India

9. NAFDAC REGISTRATION NUMBER(S)
B4 - 8602