1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 20mg Gastro-resistant Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gastro-resistant tablet contains:
20 mg Pantoprazole (as pantoprazole sodium sesquihydrate 22.6 mg).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet.

Orange coloured, enteric coated oval biconvex tablets plain on both the sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pantoprazole 20 mg gastro-resistant tablet is indicated for use in adults and adolescents 12 years of age and above for:

- Symptomatic gastro-oesophageal reflux disease.
- For long-term management and prevention of relapse in oesophagitis.

Pantoprazole 20 mg gastro-resistant tablet is indicated for use in adults for:

- 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 (see section 4.4).

4.2 Posology and method of administration

Posology:
Adults and adolescents 12 years of age and above

Symptomatic gastro-oesophageal reflux disease
The recommended oral dose is one Pantoprazole 20 mg gastro-resistant tablet per day. Symptom relief is generally accomplished within two to four weeks. If this is not sufficient, symptom relief will normally be achieved within a further four weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, taking one tablet when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

Long-term management and prevention of relapse in reflux oesophagitis
For long-term management, a maintenance dose of one Pantoprazole 20 mg gastro-resistant tablet per day is recommended, increasing to 40 mg Pantoprazole per day if a relapse occurs. Pantoprazole 40 mg gastro-resistant tablets are available for this case. After healing of the relapse the dose can be reduced again to 20 mg Pantoprazole.

Adults:
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

The recommended oral dose is one Pantoprazole 20 mg gastro-resistant tablet per day.

Special populations

Paediatric population
Pantoprazole 20 mg gastro-resistant tablets are not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group (see section 5.2).

Hepatic Impairment
A daily dose of 20 mg Pantoprazole should not be exceeded in patients with severe liver impairment see section 4.4).

Renal Impairment
No dose adjustment is necessary in patients with impaired renal function (see section 5.2).

Elderly
No dose adjustment is necessary in elderly (see section 5.2).

Method of administration
Oral use

The tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

4.3 Contraindications

Hypersensitivity to the active substance substituted benzimidazoles or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Hepatic Impairment
In patients with severe liver impairment, the liver enzymes should be monitored regularly during treatment with Pantoprazole, particularly on long-term use. In the case of a rise of the liver enzymes the treatment should be discontinued (see section 4.2).

Co-administration with NSAIDs
The use of Pantoprazole 20 mg gastro-resistant tablets 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.

Gastric malignancy
Symptomatic response to pantoprazole may mask the symptoms of gastric malignancy and may delay diagnosis. 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.

Further investigation is to be considered if symptoms persist despite adequate treatment.

Co-administration with HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, due to significant reduction in their bioavailability (see section 4.5).

Influence on vitamin B12 absorption
Pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

Long term treatment
In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Bone Fractures
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Gastrointestinal infections caused by bacteria
Treatment with Pantoprazole 20 mg gastro-resistant tablets may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella and Campylobacter* and *C. difficile.*

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life-threatening or fatal, have been reported in association with pantoprazole with frequency not known (see section 4.8). Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, pantoprazole should be withdrawn immediately and an alternative treatment considered.

Hypomagnesaemia
Severe hypomagnesaemia has been rarely reported in patients treated with PPIs like Pantoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8). In most affected patients, hypomagnesaemia and hypomagnesaemia associated hypocalcaemia and/or hypokalaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or medicinal products that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Subacute cutaneous lupus erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Pantoprazole sodium 20mg. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, Pantoprazole treatment should be stopped for at least 5 days before CgA

measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products with pH-Dependent Absorption Pharmacokinetics
Because of profound and long lasting inhibition of gastric acid secretion, Pantoprazole may interfere with the absorption of medicinal products where gastric pH is an important determinant of oral availability, e.g some azole antifungals as ketoconazole, itraconazole, posaconazole and other medicine as erlotinib.

HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir due to significant reduction in their bioavailability (see section 4.4).

If the combination of HIV protease inhibitors with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted.

Coumarin anticoagulants (phenprocoumon or warfarin)
Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Methotrexate
Concomitant use of high dose methotrexate (e.g. 300 mg) and protonpump inhibitors has been reported to increase methotrexate levels in some patients. Therefore in settings where high dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of Pantoprazole may need to be considered

Other interactions studies
Pantoprazole is extensively metabolised in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

Interaction studies with medicinal products also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions.

An interaction of pantoprazole with other medicinal products or compounds, which are metabolized using the same enzyme system, cannot be excluded.

Results from a range of interaction studies demonstrate that Pantoprazole does not effect the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption of digoxin.

There were no interactions with concomitantly administered antacids.

Interaction studies have also been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

Medicinal products that inhibit or induce CYP2C19:

Inhibitors of CYP2C19 such as fluvoxamine could increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of pantoprazole, or those with hepatic impairment.

Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John´s wort (Hypericum perforatum) may reduce the plasma concentrations of PPIs that are metabolized through these enzyme systems.

Drug-laboratory test interactions
There have been reports of false-positive results in some urine screening tests for tetrahydrocannabinol (THC) in patients receiving pantoprazole. An alternative confirmatory method should be considered to verify positive results.

4.6 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of Pantoprazole.

Animal studies have shown reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Pantoprazole during pregnancy.

Breast-feeding
Animal studies have shown excretion of Pantoprazole in breast milk. There is insufficient information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the newborns/infants cannot be excluded. Therefore a decision on whether to discontinue breast-feeding or to discontinue /abstain from Pantoprazole therapy should take into account the benefit of breast-feeding for the child, and the benefit of Pantoprazole therapy for the women.

Fertility
There was no evidence of impaired fertility following the administration of pantoprazole in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

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

Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

4.8 Undesirable effects

Approximately 5 % of patients can be expected to experience adverse drug reactions (ADRs).

The table below lists adverse reactions reported with pantoprazole, 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).

For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a “not known” frequency.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency **System Organ Class**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders			Agranulocytosis	Thrombocytopenia; Leukopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia, hypomagnesaemia (see section 4.4) Hypocalcaemia[1)], Hypokalaemia[1]
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination, Confusion, (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)
Nervous system disorders		Headache; Dizziness	Taste disorder		Parasthesia
Eye disorders			Disturbances in vision/ blurred vision		
Gastrointestinal Disorders	Fundic gland polyps (benign)	Diarrhoea; Nausea/Vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			Microscopic colitis

Hepatobiliary disorders		Liver enzymes increased (transaminases, γ-GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and subcutaneous tissue disorders		Rash/exanthema/eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson Syndrome, Lyell-Syndrome (TEN); Erythema multiforme; Photosensitivity, Subacute cutaneous lupus erythematosus (see section 4.4); Drug reaction with eosinophilia and systemic symptoms DRESS.
Musculoskeletal, connective tissue disorders		Fracture of the hip, wrist or spine (see section 4.4)	Arthralgia; Myalgia		Muscle spasm [(2)]
Renal and urinary disorders					Tubulointerstitial nephritis (TIN) (with possible progression to renal failure)
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions	Injection site thrombophlebitis	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

[1.] Hypocalcemia and/or hypokalaemia may be related to the occurrence of hypomagnesemia (see section 4.4).

[2.] Muscle spasm as a consequence of electrolyte disturbance

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard**.**

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 H_2 receptor inhibitors, treatment with pantoprazole reduced 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.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

5.2 Pharmacokinetic properties

Absorption

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 20 mg oral dose. On average at about 2.0 h - 2.5 h p.a. the maximum serum concentrations of about 1 - 1.5 µg/ml are achieved, and these values remain constant after multiple administration.

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

The absolute bioavailability from the tablet was found to be about 77 %. Concomitant intake of food had no influence on AUC, maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

Distribution
Pantoprazole's serum protein binding is about 98%. Volume of distribution is about 0.15 l/kg.

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

Elimination
Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the proton pumps of the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

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

Special Populations

Poor Metabolisers
Approximately 3 % of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60 %. These findings have no implications for the posology of Pantoprazole.

Renal impairment
No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialyzed. Although the main metabolite has a moderately delayed half-life (2 - 3 h), excretion is still rapid and thus accumulation does not occur.

Hepatic impairment
Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between three and six hours and the AUC values increased by a factor of three to five , the maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

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

Paediatric population
Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5-16 years AUC and C_{max} were in the range of corresponding values in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 - 16 years there was no significant association between pantoprazole clearance and age or weight.

AUC and volume of distribution were in accordance with data from adults.

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 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 (Cmax) 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

Tablet core:
mannitol
crospovidone
sodium carbonate, anhydrous
hydroxypropylcellulose
calcium stearate

Tablet coating:
hypromellose

yellow iron oxide (E172)
Ferric oxide red (E172)
methacrylic acid-ethylacrylate -copolymer (1:1)
triethyl citrate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Packs: Cartons containing ALU/ALU blisters and HDPE container with polypropylene cap.

Cartons of 7, 14, 15, 28, 30, 56, 60, 84, 90, 98, 100, 112, 140, 280, 500 & 700 tablets.
HDPE container of 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Brown & Burk UK Ltd
5 Marryat Close
Hounslow West
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TW4 5DQ
UK

8. MARKETING AUTHORISATION NUMBER(S)

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