CONTROLOC® 20 mg

1. Name of the Medicinal Product

Controloc 20 mg Tablets

2. Quality and Quantitative Composition

One gastro-resistant tablet contains pantoprazole sodium sesquihydrate 22.6 mg (equivalent to pantoprazole 20 mg) for oral use

3. Pharmaceutical Form

Yellow, oval, biconvex film-coated tablets with white to almost white cores, printed on one side with “P20”

4. Clinical Particulars

4.1 Therapeutic indications

Pediatric:

- Symptomatic treatment of gastroesophageal reflux disease (GERD)
- Reflux esophagitis

Adult:

- Symptomatic treatment of gastroesophageal reflux disease (GERD)
- For long-term management and prevention of relapse in reflux oesophagitis.
- Prevention of gastroduodenal ulcers induced by non-selective non-steriodal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAIDs treatment.

4.2 Posology and method of administration

General instructions

Controloc® 20 mg gastro-resistant tablets should not be chewed or crushed, and should be swallowed whole with some water.

List of therapeutic indications, posology and method of oral administration

Classification	Therapeutic Indication	Posology and method of administration
Children 5 to 11 years of age	Symptomatic gastroesophageal reflux disease	One tablet of **Controloc**® 20 mg per day. If symptom control has not been achieved after four weeks treatment with **Controloc**® 20 mg tablet daily, further investigation is recommended.
	Reflux esophagitis	≥19 kg to <35 kg: 20 mg once daily ≥35 kg: 40 mg once daily A 4-week period is usually required for the treatment of reflux esophagitis. If this is not sufficient, healing will usually be achieved within a further 4 weeks

Classification	Therapeutic Indication	Posology and method of administration
Adults and adolescents 12 years of age and above	Symptomatic treatment of gastroesophageal reflux disease (GERD)	The recommended oral dosage is one gastro-resistant tablet **Controloc**® 20 mg per day. Symptom relief is generally accomplished within 2-4 weeks, and a 4-week treatment period is usually required for healing of associated oesophagitis. If this is not sufficient, healing will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on demand treatment.
Adults and adolescents 12 years of age and above	Long-term management and prevention of relapse in reflux oesophagitis	For long-term management, a maintenance dose of one gastro-resistant tablet **Controloc**® 20 mg per day is recommended, increasing to 40 mg pantoprazole per day if a relapse occurs. **Controloc**® 40 mg is available for this case. After healing of the relapse the dosage can be reduced again to 20 mg pantoprazole.
Adults	Prevention of gastroduodenal ulcers induced by non selective non-steroidal anti-inflammatory	The recommended oral dosage is one gastro-resistant coated tablet Controloc® 20 mg per day. The use of Controloc® 20 mg as a preventive of gastroduodenal ulcers induced by non-selective non-steriodal anti-inflammatory drugs (NSAIDs) should be

	drugs (NSAIDs) in patients at risk with a need for continuous NSAIDs treatment	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.

Special Patient Populations

Elderly patients:

No dose adjustment is necessary in elderly patients.

Pediatric patients:

Controloc® is not recommended for use in children below 5 years of age due to limited data on safety and efficacy in this age group.

Impaired hepatic function:

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

Impaired renal function:

No dose adjustment is necessary in patients with impaired renal function.

4.3 Contraindications

Hypersensitivity to the active ingredients, or to any of the excipients of the product.

4.4 Special warnings and special precautions for use

Bone fracture:

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-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer.)

Clostridium difficile:

PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Hypomagnesemia:

Has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesemia include tetany, arrhythmia, and seizure. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia (see Undesirable effects 4.8).

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 Posology and method of administration 4.2).

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, nelfinavir; due to significant reduction in their bioavailability.

Methotrexate:

Concomitant use with high dose methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Gastric malignancy:

Symptomatic response to pantoprazole does not preclude the presence of gastric malignancy.

Influence on vitamin B12 absorption:

Daily treatment with any acid-suppressing medication over a prolonged period of time (several years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Cyanocobalamin deficiency should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, individuals with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if relevant clinical symptoms are observed.

Interference with Laboratory Tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, proton pump inhibitor treatment should be stopped 14 days before CgA measurements.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, including erythema multiforme, Stevens-Johnson syndrome

(SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs (see Undesirable Effects, 4.8). Discontinue pantoprazole at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Subacute Cutaneous Lupus Erythematosus (SCLE)

Proton pump inhibitors are associated in rare cases with the occurrence of subacute cutaneous lupus erythematosus (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 healthcare professional should consider stopping the product.

4.5 Interactions with other medicinal products and other forms of interactions

Other interaction studies:

Pantoprazole is extensively metabolized in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways which include oxidation by CYP3A4. Interaction studies with drugs also metabolized with these pathways, including carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin, and an oral contraceptive containing levonorgestrel and ethinyl estradiol did not reveal clinically significant interactions.

An interaction of pantoprazole with other drugs 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 affect the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), or CYP2E1 (such as ethanol) and 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.

Effects of Pantoprazole on Other Medicinal Products

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, nelfinavir; due to significant reduction in their bioavailability.

Drugs with pH-Dependent Absorption Pharmacokinetics:

Pantoprazole may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability.

Methotrexate:

Concomitant use with high dose methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Clopidogrel:

Concomitant administration of pantoprazole and clopidogrel in healthy subjects 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.

Coumarin anticoagulants (phenprocoumon or warfarin):

Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenoprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenoprocoumon 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.

Effects of other medicinal products on Pantoprazole

Drugs that Inhibit or Induce CYP2C19

Inhibitors of CYP2C19, such as fluvoxamine, would likely increase the systemic exposure of pantoprazole. Inducers of CYP2C19 may decrease the systemic exposure to pantoprazole

4.6 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 "Preclinical safety data"). The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.

Lactation:

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 breastfeeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breastfeeding to the child and the benefit of pantoprazole therapy to women.

4.7 Effects on ability to drive and use of machines

Pantoprazole is not expected to adversely affect the ability to drive or 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

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

Frequency / System Organ Class	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)
Blood and lymphatic system disorders		Agranulocytosis	Thrombocytopenia; Leukopenia; Pancytopenia	
Immune system disorders		Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders		Hyperlipidaemias Weight changes		Hyponatraemia; Hypomagnesaemia; Hypocalcemia*; Hypokalemia*

Psychiatric disorders	Sleep disorders	Depression	Disorientation	Hallucination; Confusion
Nervous system disorders	Headache; Dizziness	Taste disorders		
Eye disorders		Disturbances in vision / blurred vision		
Gastrointestinal disorders	Diarrhea; Nausea/ vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			
Hepatobiliary disorders	Liver enzymes increased	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and subcutaneous tissue disorders	Rash/ exanthema/ eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome (TEN); Drug reaction with eosinophilia and systemic symptoms (DRESS); Acute generalized exanthematous pustulosis Erythema multiforme; Photosensitivity
Musculoskeletal and connective tissue disorders		Arthralgia; Myalgia		Fracture of wrist, hip and spine

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	Asthenia, fatigue and malaise	Body temperature increased; Edema peripheral		

*Hypocalcemia and/or hypokalemia may be related to the occurrence of hypomagnesemia *(see Special Warnings and Special Precautions for use, 4.4)*

4.9 Overdose

Systemic exposure with up to 240 mg intravenously over 2 minutes was well tolerated.

As pantoprazole is extensively protein bound, it is not readily dialyzable.

In the case of 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

(1) 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 in the parietal cells.

Pantoprazole is converted to its active form in the acidic environment of 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 gastric acid-related 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 consequently 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.
The fasting gastrin values increase with pantoprazole. During 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 has only been observed 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 “Preclinical safety data”) have not been observed in humans.

An influence of long- term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid based on data observed in animal

5.2. Pharmacokinetic properties

(1) Absorption

After ingestion, pantoprazole is rapidly absorbed into the bloodstream. On average the maximum serum concentrations (C_{max}) of 1 to 1.5 µg/mL (pantoprazole 20 mg tablet) or 2 to 3 µg/mL (pantoprazole 40 mg tablet) are achieved at about 2 to 2.5 hours after administration. After single and repeated administration of pantoprazole, the pharmacokinetic characteristics of pantoprazole are very similar.
Both oral and I.V. administration of pantoprazole in the dose range of 10 mg to 80 mg result in linear serum pharmacokinetics. The absolute bioavailability from the tablet was found to be about 77%. Concomitant intake of food had no relevant influence either on the AUC or on the C_{max} and, thus, bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

With pantoprazole granules, the peak serum concentration of 1.9 mg/l is reached after 2- 2.5 hours in the fasting state. The AUC is about 5.5 mgh/l. Concomitant food intake reduces both AUC and the peak serum concentration and delays the time to peak concentration. This effect is reduced by taking pantoprazole Granules 30 minutes before breakfast.

(2) Distribution

Pantoprazole's serum protein binding is about 98%, and in keeping with this, pantoprazole has a low volume of distribution (about 0.15 l/kg) and limited tissue distribution.

(3) Metabolism

Pantoprazole is rapidly eliminated from the circulation and extensively metabolized in the liver. Metabolism occurs via oxidation by the CYP enzyme system, predominantly by CYP2C19 and CYP3A4 (Phase I metabolism, which is saturable). Pantoprazole undergoes further biotransformation by conjugation with sulphate, which involves the cytoplasmic enzyme sulphotransferase (phase II metabolism, which is not saturable), and which presents the main metabolism of pantoprazole.

(4) Excretion and elimination

About 80% of the metabolites of pantoprazole are eliminated via the renal route, the rest via the feces. None of the metabolites are considered as biologically active. The main metabolite in both the serum and urine is desmethylpantoprazole, which is conjugated with sulphate. T1/2 of the main metabolite is about 1.5 hour (which is not much longer than that of pantoprazole, 1 hour).

(5) Special populations

Impaired renal function

In patients with impaired renal function (including dialysis), pantoprazole showed no prolonged elimination half-life and no accumulation when compared with healthy subjects. No dose adjustment is necessary in patients with impaired renal function.

Impaired hepatic function

In comparison with healthy subjects, after oral administration of pantoprazole sodium to patients with liver cirrhosis classified as Child-Pugh A and B, serum elimination half-lives of pantoprazole increased to between 3 and 6 hours (pantoprazole 20 mg tablet) or 7 to 9 hours (pantoprazole 40 mg tablet and powder) and AUC values increased by a factor of 3 to 5 (pantoprazole 20 mg tablet) or 5 to 7-fold (pantoprazole 40 mg tablet and powder). Maximum serum concentrations, C_{max}, in these patients increased only slightly (1.3-fold after oral administration, 1.5-fold after I.V. application) relative to healthy subjects. The observed pharmacokinetic changes did not lead to relevant accumulation following once-daily dosing.

Age, Gender, Race

As with other clinically used PPIs, a small percentage of the population (about 3% Caucasians, 20% Asians) shows slower elimination of pantoprazole ($T_{1/2}$ being up to 10 hours as compared with 1hour). Such persons are known as poor metabolizers as a result of a deficiency of the CYP2C19 enzyme. In these individuals the metabolism of pantoprazole is probably mainly catalyzed 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 metabolizers than in subjects having a functional CYP2C19 enzyme

(extensive metabolizers). Mean peak plasma concentrations were increased by about 60 %. These findings have no implications for the posology of pantoprazole.

Results from several studies in children/adolescents from birth to 16 years indicate that the pharmacokinetics of pantoprazole is similar to those in adults when appropriately adjusted by patient weight, despite somewhat decreased clearance in patients less than 1 year old. Similar to adults, pediatric patients who were poor metabolizers of CYP2C19, exhibited reduced clearance that was more than 70% lower than the typical value.

Compared with younger subjects, slight increases in AUC and C_{max} were noted after single and repeated oral administration of pantoprazole to healthy elderly subjects (age >65 years). However, no dose adjustment is necessary in elderly patients.

(6) Drug Interactions

Pantoprazole is metabolized in the liver via the CYP enzyme system. An interaction of pantoprazole with other drugs or compounds, which are metabolized using the same enzyme system, cannot be ruled out. Nevertheless, in specific tests pantoprazole did not affect the clearance of several compounds metabolized by CYP enzymes. Vice-versa, all drugs that were tested regarding their potential influence on the pharmacokinetics of pantoprazole had no relevant effect.

No detectable interactions between pantoprazole and any other commonly prescribed co-medication tested so far were found.

Metabolism of pantoprazole occurs via oxidation by the CYP enzyme system, predominantly by CYP2C19 and CYP3A4. Interaction studies with drugs also metabolized by these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin, and an oral contraceptive containing levonorgestrel and ethinyl estradiol did not reveal clinically significant interactions. Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolized by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), or CYP2E1 (such as ethanol) and 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.

5.3. Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 it can be concluded 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.

Animal Toxicology and/or Pharmacology

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 to the thyroid glands are expected.

In animal reproduction studies, signs of fetotoxicity were observed at doses above 3 mg/kg.
Investigations revealed no evidence of impaired fertility or teratogenic effects. Crossing of the placenta was investigated in the rat and was found to increase with
advanced gestation. As a result, the concentration of pantoprazole in the fetus is increased shortly before birth.

6. Pharmaceutical Particulars

6.1. List of excipients

Excipient(s)

Core: Sodium carbonate, anhydrous; Mannitol; Crospovidone; Povidone K90; Calcium stearate, vegetable

Coating: Hypromellose 2910; Povidone K25; Titanium dioxide (E171); Yellow ferric oxide (E172); Propylene glycol; Methacrylic Acid – Ethyl Acrylate Copolymer (1:1); Sodium laurilsulfate; Polysorbate 80; Triethyl citrate

Printing ink brown: shellac, red, black and yellow iron oxide (E172), Ammonia solution, concentrated

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

See expiry date on outer carton.

6.4. Special precautions for storage

Keep out of the reach of children.

6.5. Nature and contents of container

Alu-Alu blisters of 14 tablets per carton.

7. Marketing Authorization Holder

Manufactured by:

TAKEDA GMBH, Oranienburg, Germany

Imported by

TAKEDA (THAILAND), LTD., Bangkok, Thailand

8. Marketing Authorization Numbers

1C 13/56 (N)

9. Date of authorization

15 January 2013

10. Date of revision of the text

Aug 2022