Instructions for Use

1. Name of the Medicinal Product

Controloc® 20 mg
Controloc® 40 mg
Controloc® i.v

2. Qualitative and Quantitative Composition

Controloc® 20 mg
1 gastro-resistant (enteric coated) tablet contains 20 mg pantoprazole (as pantoprazole sodium) for oral use. Active ingredient: 20mg pantoprazole (as pantoprazole sodium sesquihydrate 22.6 mg)

Controloc® 40 mg
1 gastro-resistant (enteric coated) tablet contains 40 mg pantoprazole (as pantoprazole sodium) for oral use. Active ingredient: 40mg pantoprazole (as pantoprazole sodium sesquihydrate 45.1 mg)
Controloc® i.v

1 vial contains 40 mg pantoprazole (as pantoprazole sodium) as powder for solution for injection. Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per vial. Active ingredient: 40mg pantoprazole (as pantoprazole sodium 42.3 mg)

3. Pharmaceutical Form

Controloc® 20 mg
Gastro-resistant tablets, yellow, oval, biconvex, “P20” in brown printing ink
Packs with 7 and 14 gastro-resistant tablets

Controloc® 40 mg
Gastro-resistant tablets, yellow, oval, biconvex, “P40” in brown printing ink
Packs with 7and 14 gastro-resistant tablets

Controloc® i.v
Powder for solution for injection

Packs of 1 vial with 42.3mg white to off-white powder

4. Clinical Particulars

4.1. Therapeutic indications

Controloc® 20 mg
- Mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing).
- Long-term management and prevention of relapse in reflux oesophagitis.
- 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.

Controloc® 40 mg

- In combination with two appropriate antibiotics (see Dosage) for the eradication of H.pylori in patients with peptic ulcers with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism.
- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux oesophagitis

Controloc® i.v
Short term use for symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:

- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux esophagitis

4.2. Posology and method of administration

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

Therapeutic Indication	**Posology and method of oral administration**
Mild reflux disease and associated Symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)	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.
Long-term management and prevention of relapse in reflux oesophagitis	For long-term management, a maintenance dose of one gastroresistant 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.
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 dosage is one gastro-resistant coated tablet Controloc 20mg per day. The use of pantoprazole 20 mg as a preventive of gastroduodenal ulcers induced by non-selective nonsteroidal 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

Controloc® 40 mg
Controloc 40 mg gastro-resistant tablets should not be chewed or crushed, and should be swallowed whole with water

Therapeutic Indication	**Posology and method of oral administration**
Eradication of H.pylori in combination with appropriate antibiotics	In Helicobacter pylori positive patients with gastric and duodenal ulcers, eradication of the germ by a combination therapy should be achieved. Depending upon the resistance pattern, the following combinations can be recommended for the eradication of *H. pylori*: a) twice daily one tablet Controloc 40mg + twice daily 1000 mg amoxycillin + twice daily 500 mg clarithromycin b) twice daily one tablet Controloc 40mg + twice daily 500 mg metronidazole + twice daily 500 mg clarithromycin c) twice daily one tablet Controloc 40mg + twice daily 1000 mg amoxycillin + twice daily 500 mg metronidazole In combination therapy for eradication of Helicobacter pylori infection, the second Controloc 40mg tablet should be taken before the evening meal. The combination therapy is implemented for 7 days in general and can be prolonged to up to two weeks maximum. If, to ensure healing of the ulcers, further treatment with pantoprazole is indicated, the dosage recommendations for duodenal and gastric ulcers should be considered. A duodenal ulcer generally heals within 2 weeks. If a 2-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks. A 4-week period is usually required for the treatment of gastric ulcers and reflux esophagitis. If this is not sufficient, healing will usually be achieved within a further 4 weeks.
Treatment of gastric ulcer and duodenal ulcer	If combination therapy is not an option, e.g. if the patient has tested negative for Helicobacter pylori, the following dosage guidelines apply for Controloc 40 mg monotherapy:

	For the treatment of gastric and duodenal ulcer and reflux esophagitis one tablet of Controloc 40mg per day. In individual cases the dose may be doubled (increase to 2 tablets Controloc 40mg daily) especially when there has been no response to other treatment.

Controloc® i.v

The intravenous administration of Controloc i.v. is recommended only if oral application is not appropriate.

Therapeutic Indication	**Posology and method of IV administration**
Duodenal ulcer, gastric ulcer, moderate and severe reflux esophagitis	The recommended intravenous dosage is one vial (40 mg pantoprazole) Controloc i.v. per day. As soon as oral therapy is possible, treatment with Controloc i.v. should be discontinued and 40 mg pantoprazole p. o. should be administered instead. This medicine should be administered by a healthcare professional and under appropriate medical supervision. Intravenous administration of pantoprazole is recommended only if oral administration is not appropriate. Data are available on intravenous use for up to 7 days. **Method of administration** Pantoprazole should be administered intravenously after reconstitution, or reconstitution and dilution. A ready-to-use solution is prepared by injecting 10 ml of physiological sodium chloride solution for injection. The prepared solution may be administered directly or may be administered after mixing it with 100 ml physiological sodium chloride solution for injection or 5% Glucose solution for injection. After preparation, the solution must be used within 12 h. The medicinal product should be administered intravenously over 2 - 15 minutes. **General instructions** Keep the vial in the outer carton in order to protect from light. As soon as oral therapy is possible, treatment with pantoprazole i.v. should be discontinued and 40 mg pantoprazole p. o. (by mouth) should be administered instead.

Special Patient Populations

Pediatric patients:
The experience in children is limited. Pantoprazole 20mg and 40mg tablet is not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group. Pantoprazole 40mg powder for solution for injection is not recommended for use in patients below 18 years of age.

Impaired hepatic function:
A daily dose of Pantoprazole 20mg should not be exceeded in patients with severe liver impairment (See section 4.4)

In addition, pantoprazole 40 mg tablet must not be used in combination treatment (e.g. amoxicillin, clarithromycin,) for eradication of *H. pylori* in patients with moderate to severe hepatic dysfunction since currently no data are available on the efficacy and safety of pantoprazole in combination treatment of these patients (See section 4.3).

Impaired renal function:
No dose adjustment is necessary in those with impaired renal function.

In addition, pantoprazole 40 mg tablet must not be used in combination treatment (e.g. amoxicillin, clarithromycin) for eradication of *H. pylori* in patients with impaired renal function, since currently no data are available on the efficacy and safety of pantoprazole in combination treatment for these patients.

Elderly patients:
Generally, no dose adjustment is necessary in elderly patients. However, the daily dose of 40mg should not be exceeded in treatment of gastric or duodenal ulcer.

4.3 Contraindications

Controloc should generally not be used in cases of known hypersensitivity to one of the other constituents of Controloc 20 mg, Controloc 40mg tablet and Controloc i.v. or of the combination partners.

Controloc 40mg tablet must not be used in combination treatment for eradication of *H.pylori* in patients with moderate to severe liver or kidney function disturbances since currently no clinical data are available on the efficacy and safety of Controloc 40mg in combination treatment of these patients.

4.4 Special warnings and precautions for use

The intravenous administration of Controloc i.v. is recommended only if oral application is not appropriate

In presence of alarm symptoms
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.

Hepatic Impairment

In patients with severe liver impairment the daily dose has to be reduced to 20mg pantoprazole. In patients with severe liver impairment, liver enzymes should be monitored during therapy regularly. In the case of a rise of the liver enzymes, the treatment should be discontinued. (See Dosage and Method of Administration).

Gastrointestinal infections caused by bacteria, including Clostridium difficile

Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with Controloc may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella and Campylobacter.* In hospitalized patients, PPI therapy may be associated with an increased risk of *Clostridium difficile* infection.

Published observational studies suggest that proton pump inhibitor (PPI) therapy like pantoprazole may be associated with an increased risk of Clostridium difficile-associated diarrhoea (CDAD), especially in hospitalised patients. This diagnosis should be considered for diarrhoea that does not improve (see 4.8 Undesirable Effects). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with Controloc, refer to Warnings and Precautions sections of those package inserts.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious manifestations of hypomagnesamia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmias can occur but they may begin insidiously and be overlooked. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia. In most patients, treatment of hypomagnesemia (and hypomagnesemia associated hypocalcemia and/or hypokalemia) 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 hypomagnesaemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically. [See Undesirable effects].

Bone Fractures

Several published observational studies suggest 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 (see Dosage and Administration and Undesirable effects).

Concomitant use with Methotrexate

Literature suggests 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 (see Drug Interactions).

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.

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 section 4.8). Discontinue pantoprazole at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE)

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from

young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving pantoprazole, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., Antinuclear antibody) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Co-administration with NSAIDs (Applies to Controloc® 20mg only)
The use of Controloc 20mg as a preventive of gastroduodenal ulcers induced by non-selective nonsteroidal 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 gastro-intestinal bleeding.

Combination therapy (Applies to Controloc® 40mg only)
In the case of combination therapy, the prescribing information for the respective drugs must be observed.

Long term treatment (Applies to Controloc® 20mg and 40mg only)
In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs with pH-Dependent Absorption Pharmacokinetics:
Controloc may reduce or increase the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole)

HIV medications (e.g. atazanavir)
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.

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailibility of atazanavir. The absorption of atazanavir is pH dependent.

Coumarin anticoagulants (phenprocoumon or warfarin)
Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in International Normalised Ratio (INR) and prothrombin have been reported during concomitant treatment in the post-marketing period. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death. Therefore, in patients treated with coumarin anticoagulants (e.g. phenprocoumon or warfarin), monitoring of increase prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) 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 conducted (see Warnings and Precautions).

Other interactions studies

Pantoprazole is metabolized 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.

An interaction of pantoprazole with other drugs or compounds which are metabolized using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in interaction studies with drugs also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, phenytoin and an oral contraceptive containing levonorgestrel and ethinyl oestradiol.

Results from a range of interaction studies demonstrate that pantoprazole does not effect the metabolism of active substances metabolised 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 also no interactions with concomitantly administered antacids.

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

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.

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

The limited data from the use of pantoprazole in pregnant women does not indicate foetal /neonatal toxicity. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Controloc 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 breast-feeding or to continue/discontinue therapy with Controloc should be made taking into account the benefit of breastfeeding to the child, and the benefit of Controloc therapy to women.

4.7 Effects on the 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

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

The most commonly reported ADRs are diarrhoea and headache, both occurring in approximately 1

% of patients.

Table 1 lists adverse drug reactions reported with pantoprazole in clinical studies and post-marketing experience. The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines:

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 Organ class	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
Blood and lymphatic system			Agranulocytosis	Leukopenia; Thrombocytopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions including anaphylactic shock)		Systemic lupus erythematosus
Metabolism and nutrition disorders			Hyperlipidaemia; 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		Diarrhoea 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; Toxic epidermal necrolysis; DRESS^; Acute generalized exanthematous pustulosis; Erythema multiforme; Photosensitivity, Cutaneous lupus erythematosus
Musculoskeletal, 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			Gynecomastia		
General disorders and administration site conditions	Injection site thrombophle-bitis[+]	Asthenia; Fatigue and Malaise	Body temperature increased; Peripheral oedema		

[+] Applicable to Controloc i.v. only

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

^DRESS: Drug Rash with Eosinophilia and Systemic Symptoms

4.9 Overdosage

Systemic exposure with doses up to 240 mg administered 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, the usual rules of intoxication therapy apply.

4.10 Drug abuse and dependence

Drug dependence has not been observed

5. Pharmacological Properties

Controloc: contains Pantoprazole, a proton pump inhibitors which inhibits the gastric H^+K^+ ATPase which is responsible for acid secretion in the parietal cells of the stomach. Pantoprazole is white to off-white powder with a molecular weight of 432.4. Pantoprazole is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane. Pantoprazole is a racemic mixture with a melting point of 138° C.

The chemical name for Pantoprazole is sodium-5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2- pyridinyl)methyl] sulfinyl]-1 H-benzimidazole sesquihydrate and is represented by the following chemical structure :

Empirical chemical structure: $C_{16}H_{14}F_2N_3NaO_4Sx1.5H_2O$

5.1 Pharmacodynamic properties
Pharmacotherapeutic / indication group / action mechanism
Selective proton pump inhibitor, substituted benzimidazole

(1) Mechanism of Action
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells. Pantoprazole is converted to its active form in the acidic canaliculi 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 in 2 weeks. As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in 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, the substance can affect hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the active substance is given orally or intravenously. The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the normal upper limit. 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 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 and liver enzymes according to results in animal studies.

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.

(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. $T_{1/2}$ 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 reduction is requested when pantoprazole is administered to patients with restricted kidney function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole can be dialyzed. Although the main metabolite has a moderately delayed half-life (2

- 3h), excretion is still rapid and thus accumulation does not occur.

Impaired hepatic function

*Although fo*r patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 3 and 6 h (pantoprazole 20 mg tablet) and the AUC values increased by a factor of 3 – 5 (pantoprazole 20 mg tablet), the maximum serum concentration only increased slightly by a factor of 1.3 (after oral administration) compared with healthy subjects.

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

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.

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 generally 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), or does not interfere with pglycoprotein 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.

(See Interaction with other medicinal products and other forms of interaction).

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 side 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

Controloc® 20 mg and Controloc® 40 mg
Sodium carbonate; mannitol; crospovidone; povidone K 90; calcium stearate; hypromellose; povidone K 25; propylene glycol; methacrylic acid-ethylacrylate-copolymer (1:1); polysorbate 80; sodium laurylsulphate; triethyl citrate; colours (E 171 and E 172); printing ink

Controloc® i.v
Disodium edetate; sodium hydroxide

Each vial contains: 1 mg disodium edetate and 0.24 mg sodium hydroxide. This medicinal product contains less than 1 mmol sodium (23 mg) per vial.

6.2. Incompatibilities *(Applies to Controloc® i.v only)*

This medicinal product must not be mixed with other medicinal products except those mentioned in section "Special precautions for disposal**".**

6.3 Storage conditions and shelf life

Controloc® 20 mg
Controloc 20 mg gastro-resistant tablets stored below 30°C remain unchanged for 3 years.

The expiry date of this pack is printed on the Container and on the folding box. Do not use this pack after the expiry date.

Controloc® 40 mg
Controloc 40 mg gastro-resistant tablets stored below 25°C remain unchanged for 3 years.

The expiry date of this pack is printed on the Container and on the folding box. Do not use this pack after the expiry date.

Controloc® i.v
2 years. The reconstituted solution must be used within 12 hours after preparation. Controloc i.v. should be stored below 25°C. Keep container in the outer carton.

The expiry date of this pack is printed on the container and on the folding box. Do not use this pack after the expiry date.

Keep the vial in the outer carton in order to protect from light.

6.4 Instructions for use/ handling *(Applies to Controloc® i.v only)*

A ready-to-use solution is prepared by injecting 10 ml of physiological sodium chloride solution (0.9%) into the vial containing the dry substance (powder). The appearance of the product after reconstitution is a clear yellowish solution. This solution may be administered directly or may be administered after mixing with 100 ml physiological sodium chloride

(0.9%) solution for injection or 5% Glucose solution for injection. Glass or plastic containers should be used for dilution.

After preparation, the solution must be used within 12 h. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at not more than 25° C.

Controloc i.v. should not be manufactured or mixed with solvents other than those stated. The drug should be administered intravenously over 2 -15 minutes.

Any product that has remained in the container or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed) has to be discarded.

The contents of the vial is for single use only.

*Any un*used product or waste material should be disposed in accordance with local requirements.

7. Product Owner

Takeda GmbH, Konstanz, Germany

8. Date of Revision

July 2022 (updated according to CCDS v9.0)