CONTROLOC® 40 mg
Gastro-resistant tablets
Active ingredient: Pantoprazole sodium sesquihydrate

NAME AND STRENGTH OF ACTIVE SUBSTANCES

Each gastro-resistant tablet contains 45.1mg pantoprazole sodium sesquihydrate (corresponding to 40mg pantoprazole) and the following excipients:
Sodium carbonate; Mannitol; Crospovidone; Povidone K90; Calcium stearate; Hypromellose 2910; Povisone K25; Titanium dioxide E171; Yellow ferric oxide E172; Propylene glycol; Triethyl citrate; Methaacrylic acid – ethyl acrylate Copolymer (1:1); Polysorbate 80; Sodium Laurisulfate; Printing ink.

PRODUCT DESCRIPTION

Gastro-resistant tablet.
Yellow, oval, biconvex film-coated tablet imprinted with "P40" in brown ink on one side.

PHARMACOLOGICAL PROPERTIES

Pharmcodynamics Properties

Pharmacotherapeutic / indication group / action mechanism

Selective proton pump inhibitor, substituted benzimidazole, ATC code: A02BC02

Mechanism of action

Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H+, K+-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved within 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.

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 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.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum CgA levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors.
Available published evidence suggests that proton pump inhibitors should be discontinued 14 days prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

Pharmacokinetics Properties

Absorption

After ingestion, pantoprazole is rapidly absorbed into the bloodstream. On average the maximum serum concentrations (Cmax) 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 Cmax 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.

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.

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.

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).

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, Cmax, 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 (T1/2 being up to 10 hours as compared with 1 hour). 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 Cmax 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.

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.

Preclinical safety data
Carcinogenesis, Mutagenesis, Impairment of Fertility
Preclinical 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.
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 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.

INDICATIONS

- In combination with two appropriate antibiotics (see “Posology”) for the eradication of Helicobacter 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 cases of inflammation of the esophagus (reflux esophagitis)
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions

POSOLOGY AND METHOD OF ADMINISTRATION

The following information applies unless Controloc 40 mg has been otherwise prescribed by your doctor. Please follow these instructions, as otherwise Controloc 40 mg may not have the desired effect!

Adults and adolescents 12 years of age and above:

<u>Treatment of moderate and severe reflux oesophagitis</u>

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.

Adults:

Eradication of H. pylori in combination with two appropriate antibiotics

In cases of duodenal or gastric ulcer in which infection with Helicobacter pylori has been confirmed, the microorganism should be eradicated by combination treatment. Depending on the resistance pattern, the following combinations are recommended:

a) 2 x 1 Controloc 40 mg gastro-resistant tablet / day
   + 2 x 1000 mg amoxicillin / day
   + 2 x 500 mg clarithromycin /day

b) 2 x 1 Controloc 40 mg gastro-resistant tablet / day
   + 2 x 500 mg metronidazole / day
   + 2 x 500 mg clarithromycin / day

c) 2 x 1 Controloc 40 mg gastro-resistant tablet / day
   + 2 x 1000 mg amoxicillin / day
   + 2 x 500 mg metronidazole / day

Treatment of gastric and duodenal ulcer

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.

Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions

For the long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions patients should start their treatment with a daily dose of 80 mg (2 tablets of “Controloc 40mg” 40 mg). Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control. Treatment duration in Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

Children below 12 years of age:

Controloc 40mg is not recommended for use in children below 12 years of age due to limited data in this age group.

Type and duration of treatment

Combination therapy for eradication of Helicobacter pylori infection usually lasts 7 days and can be extended to a maximum of 2 weeks. If after this time further treatment with Controloc 40 mg is indicated to ensure that the ulcer heals completely, the dose recommendations for gastric and duodenal ulcers must be

observed. In the majority of cases, a duodenal ulcer heals completely within 2 weeks. If a two-week treatment period is not sufficient, healing will be achieved in almost all cases within a further 2 weeks. Gastric ulcers and reflux esophagitis usually require a 4-week course of treatment. If this should be inadequate, healing will in most cases be achieved within a further 4 weeks. Treatment should not exceed 8 weeks as experience with long-term use is limited. Treatment duration in Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

Instructions for use / handling

Controloc 40 mg gastro-resistant tablets must not be chewed or crushed and must be swallowed whole with water. In combination therapy for eradication of Helicobacter pylori infection the second Controloc 40 mg tablet should be taken before the evening meal.

Special Patient Populations

Impaired hepatic function:

A daily dose of 20 mg pantoprazole (1 tablet of 20 mg pantoprazole or half a vial of 40 mg pantoprazole I.V.) should not be exceeded in patients with severe liver impairment.

Impaired renal function:

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

CONTRAINDICATIONS

Controloc 40 mg must not be used in combination treatment for eradication of Helicobacter 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 40 mg in combination treatment of these patients. Controloc 40 mg should generally not be used in cases of known hypersensitivity to one of the constituents of Controloc 40 mg or of the combination partners.

SPECIAL WARNINGS AND 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).

Observational studies suggest PPI 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.

***Clostridium difficile**:*
PPI therapy may be associated with an increased risk of *Clostridium difficile associated diarrhea,* especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

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 such as fatigue, tetany, delirium, convulsions, dizziness, arrhythmia, and seizure can occur but they may begin insidiously and be overlooked. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia (see Undesirable Effects). In most affected patients, hypomagnesaemia (and hypomagnesemia associated hypocalcemia and/or hypokalemia) improved after magnesium replacement and discontinuation of the PPI.
For patient expected to be on prolonged treatment or who take PPIs with medications such digoxin or drugs that may cause hypomagnesemia (e.g. diuretics), health care professionals may consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

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.

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
In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment (e.g., longer than 3 years), 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.

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.

Regular Surveillance

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

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*). 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.

Pregnancy and lactation

The limited data on 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. Pantoprazole should not be used during pregnancy unless clearly necessary.
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.

Effects on the ability to drive and to use 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. If affected,
patients should not drive or operate machines.

INTERACTIONS

Drugs with pH-Dependent Absorption Pharmacokinetics:

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

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.

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) 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.

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 (tacrolimus, fluvoxamine):
Concomitant administration of pantoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.
Inhibitors of CYP2C19, such as fluvoxamine, would likely increase the systemic exposure 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.

UNDESIRABLE EFFECTS
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.

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

Frequency / Organ System	Common	Uncommon	Rare	Very Rate	Not known
Blood and lymphatic system disorders			Agranulocytosis	Thrombocytopenia; Leukopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including		

Frequency / Organ System	Common	Uncommon	Rare	Very Rate	Not known
			anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemias; weight changes		Hyponatraemia; Hypomagnesaemia; Vitamin B12 deficiency; 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	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	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and sub-cutaneous tissue disorders		Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens- Johnson-Syndrome; Toxic epidermal necrolysis; Drug reaction with eosinophilia and systemic

Frequency / Organ System	Common	Uncommon	Rare	Very Rate	Not known
					symptoms; Acute generalized exanthematous pustulosis; Erythema multiforme; Photosensitivity; Subacute cutaneous lupus erythematosus;
Musculoskeletal, connective tissue disorders		Fracture of the hip, wrist or spine	Arthralgia; Myalgia		
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; Oedema peripheral		
Infections & infestations					*Clostridium difficile* associated diarrhea

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

OVERDOSAGE

Systemic exposure with 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, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

STORAGE CONDITIONS AND SHELF LIFE

Controloc 40 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!

PACKAGING AVAILABLE

Gastro-resistant tablets Packs with 7, 14 and 28 tablets
Not all pack sizes may be marketed.

Manufacturer

Takeda GmbH
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Lehnitzstrasse 70-98
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Germany

Product Registration Holder

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