SUMMARY OF PRODUCT CHARACTERISTICS

CONTROLOC®

Trade name: Controloc®

International non-proprietary name (INN): pantoprazole

Dosage form: tablets gastro-resistant film-coated

Composition

Each tablet 20 mg contains

Core

Active substance: pantoprazole sodium sesquihydrate 22.57 mg equivalent to pantoprazole 20 mg.

Excipients: anhydrous sodium carbonate 5.00 mg; mannitol 21.33 mg; crospovidone 25.00 mg; povidone K90 2.00 mg; calcium stearate 1.60 mg; purified water 4.50 mg;

Coating

Hypromellose-2910 11.88 mg; povidone K25 0.24 mg; titanium dioxide E 171 0.21 mg; colorant yellow iron oxide E 172 0.02 mg; propylene glycol 2.66 mg; dispersion of a copolymer of methacrylic acid and ethyl acrylate [1: 1] * 8.18 mg; triethyl citrate 0.82 mg.

* Composition of 30% dispersion of a copolymer of methacrylic acid and ethyl acrylate [1: 1]: methacrylic acid and ethyl acrylate copolymer [1: 1] 7.94 mg; polysorbate 80 0.18 mg; sodium lauryl sulfate 0.06 mg;

Opacode S-1-16530 Brown printing ink: shellac 0,036 mg; colorant iron oxide (E172) red 0,009 mg; colorant iron oxide (E172) black 0,009 mg; colorant iron oxide (E172) yellow 0,0009 mg; ammonia solution concentrated 25% 0,001 mg.

Identification

Oval biconvex, yellow film-coated tablet with a white to off-white core and with brown ink imprinting "P20" on one side.

Pharmacotherapeutic group: gastric gland secretion suppressing agents – proton pump inhibitors

ATC Code: A02BC02

Pharmacological properties

Pharmacodynamics

Proton pump inhibitor (H+ K+ ATPase). Blocks the terminal stage of hydrochloric acid secretion irrespective of the irritant nature.

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 activity, i.e. blocks the final stage in the production of hydrochloric acid in the stomach. The inhibition of activity is dose-dependent and in result both basal and stimulated acid secretion decreases. As with other proton pump inhibitors and H2 receptor blockers, 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 distally to the cell receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin).

Also, the content of chromogranin A (CgA) in the serum increases due to a decrease in the secretion of hydrochloric acid. Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours.

Antisecretory activity. Reduction of gastric acid secretion by 24% occurs within 2.5-3.5 hours and 26% within 24.5-25.5 hours after the first oral administration of 20 mg Controloc®. The antisecretory activity increases up to 56% within 2.5-3.5 hours and up to 50 % within 24.5-25.5 hours after oral administration of pantoprazole once daily per 7 days. In patients with duodenal ulcer associated with *Helicobacter pylori*, the reduced gastric secretion increases the microbial sensitivity to antibiotics. The gastrointestinal motility is not affected. The secretory activity returns to normal in 3-4 days after the drug discontinuation.

Compared to other proton pump inhibitors, Controloc® is more chemically stable at neutral pH and has a less potential of interaction with the hepatic oxidase system which depends on cytochrome P450. Therefore, the clinically significant interaction of Controloc® with many other drug products has not been observed.

Pharmacokinetics

Pantoprazole is rapidly absorbed after oral administration. The maximum plasma concentration (C_{max}) during oral administration is achieved after the first dose of 20 mg already. The mean C_{max}

of 1.0 – 1.5 mcg/mL is reached after 2 – 2.5 hours after administration and maintains at this level after repeated dosing of the drug.

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

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

Pantoprazole binding to plasma proteins is 98%. Volume of distribution is about 0.15 l/kg.

The substance is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation; other metabolic pathway includes oxidation by CYP3A4.

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

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

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

Pantoprazole does not require dose reduction in patients with impaired renal function (including patients on hemodialysis). In such patients, like in healthy individuals, pantoprazole has a short terminal half-life. Only very small amounts of pantoprazole are dialyzed. Although the main metabolite has a moderately delayed half-life (2-3 h), excretion is still rapid and thus accumulation does not occur.

In patients with hepatic cirrhosis (Child-Pugh Class A and B), the terminal half-life is increased to 3-6 hours and the AUC values increased by a factor of 3-5, the maximum serum concentration only increased slightly by a factor of 1.3 for 20 mg pantoprazole compared with healthy subjects. A slight increase in AUC and Cmax in elderly volunteers compared with younger counterparts is also not clinically relevant.

Indications for use

Treatment of gastro esophageal reflux disease symptoms of mild severity (such as heartburn, regurgitation of acidic content) in adults.

Contraindications

- hypersensitivity to any of the drug components, substituted benzimidazoles;
- dyspepsia of neurotic genesis;
- co-administration of pantoprazole is contraindicated with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, nelfinavir;
- age below 18 years;
- pregnancy, lactation period.

Fertility, pregnancy and lactation

Pregnancy

Due to no data are available on using pantoprazole in pregnant women, as a safety measure Controloc® should not be used during pregnancy.

Breast-feeding

Pantoprazole and its metabolites were found in breast milk. The effect of pantoprazole on newborns / infants is unknown. Controloc® should not be used during lactation. If it is necessary to use the drug during lactation, breastfeeding should be discontinued.

Fertility

There was no evidence of impaired fertility following the administration of pantoprazole in animal studies.

Posology and administration

1 tablet (20 mg) of Controloc® is taken orally once daily before meal. Do not chew or crush the tablet, swallow it whole with a sufficient amount of water.

To reach improvement in symptoms, the drug may be necessary to take for 2-3 days, while the complete relief of symptoms requires taking the drug for 7 days. In case of worsening of relation during first 3 days of treatment specialist consultation is recommended.

Treatment should be discontinued once complete relief of symptomsis achieved .

The treatment should not exceed 4 weeks without consulting a doctor.

If no improvement is observed during 2 weeks of continuous treatment with the drug, consult the doctor.

Controloc® should not be taken for prevention purposes.

Side effects

Administration of Controloc® according to indications and at recommended doses very rarely results in side effects. The most common adverse reactions include diarrhea and headache which occur in about 1% of patients.

Below are given reported adverse reactions according to their incidence rate:

Very common *> 1/10*

Common *> 1/100 and < 1/10*

Uncommon *> 1/1,000 and < 1/100*

Rarely *> 1/10,000 and < 1/1,000*

Very rarely *< 1/10,000 including isolated cases*

Unknown incidence (non-evaluable based on available data).

Blood and lymphatic system disorders:

Rarely:

Agranulocytosis

Very rarely:

Thrombocytopenia, leukopenia, pancytopenia.

Nervous system disorders:

Uncommon:

Headache, dizziness.

Rare:

Taste disorders

Unknown incidence:

Parasthesia

Eye disorders:

Rarely:

Vision disturbances/blurred vision.

Gastrointestinal disorders:

Common:

Fundic gland polyps (benign)

Uncommon:

Diarrhea, nausea/vomiting, bloating and flatulence, constipation, dry mouth, abdominal pains.

Uncommon:

Microscopic colitis.

Renal and urinary tract disorders:

Unknown incidence:

Interstitial nephritis (with possible progression to renal failure).

Skin and subcutaneous tissue disorders:

Uncommon:

Exanthem/rash, itching, eruption.

Rarely:

Urticaria, angioedema.

Unknown incidence:

Malign exudative erythema (Stevens-Johnson syndrome), erythema multiforme, toxic epidermal necrolysis, photosensitivity, subacute cutaneous lupus erythematosus.

Musculoskeletal and connective tissue disorders:

Uncommon:

Fracture of the hip, wrist or spine

Rarely:

Arthralgia, myalgia.

Metabolism disorders:

Rarely:

Hyperlipidemia and lipid increases (triglycerides, cholesterols), change in body weight.

Unknown incidence:

Hyponatremia, hypomagnesemia, hypocalcaemia[1].

General disorders:

Uncommon:

Asthenia, fatigue and malaise.

Rarely:

Body temperature increased, peripheral oedema.

Immune system disorders:

Rarely:

Hypersensitivity (including anaphylactic reactions and anaphylactic shock).

Hepatic and biliary disorders:

Uncommon:

Elevated level of hepatic enzymes (transaminase, γ- glutamyltransferase).

Rarely:

Increased bilirubin.

Unknown incidence:

Hepatocellular injury, jaundice, hepatocellular failure.

Reproductive system and breast disorders:

Rare:

Gynecomastia

Mental disorders:

Uncommon:

Sleep disturbance.

Rarely:

Depression (including exacerbation of existing disorders).

Very rarely:

Disorientation (including exacerbation of existing disorders).

Unknown incidence:

Hallucinations, confusion (especially in predisposed patients) and possible recurrence of symptoms existing before beginning the therapy.

1 Hypocalcemia combined with hypomagnesemia.

Overdose

Up to date, no cases of overdose resulting from Controloc® administration were reported. Doses up to 240 mg were given intravenously for 2 minutes and were well tolerated.

Nonetheless, symptomatic and maintenance therapy is indicated in case of overdose and in the presence of clinical presentations only. Pantoprazole is not eliminated by hemodyalisis.

Interaction with other drugs

Concurrent treatment with other proton pump inhibitors or H2 receptors is not recommended.

Concurrent administration of Controloc® may decrease absorbance of drugs with stomach pH-dependent bioavailability (for example, ferric salts, ketoconazole, itraconazole, posaconazole and other medicine such as erlotinib).

In contrast to other proton pump inhibitors, Controloc® may be prescribed with no risk of drug interaction:

- to patients with cardiovascular diseases taking cardiac glycosides (digoxin), slow calcium channel blockers (nifedipine), beta-adrenergic blockers (metoprolol);
- to patients with gastrointestinal diseases taking antacids,antibiotics (amoxicillin, clarithromycin, metronidazole);
- to patients taking oral contraceptives containing levonorgestrel and ethinyl estradiol;
- to patients taking nonsteroidal anti-inflammatory drugs (diclofenac, naproxen, piroxicam);
- to patients with endocrine diseases taking glibeclamide, levothyroxine;
- to patients with anxiety conditions and sleep disturbances taking diazepam;
- to patients with epilepsy taking carbamazepine and phenytoin;
- to patients taking indirect anticoagulants such as warfarin and phenprocoumon with control of prothrombin time and INR at the initiation and end of treatment, and also during non-regular intake of pantoprazole; 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.

In addition, no clinically significant interaction with caffeine, ethanol or theophyllinum was observed.

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

Special precautions

Before starting treatment with Controloc®, a malignant disease must be excluded as the drug may mask the symptoms and delay the correct diagnosis.

Patients undergoing endoscopy or a urea breath test must first consult the doctor.

Patients must consult the doctor in the following cases:

- unintended weight loss, anemia, gastrointestinal bleeding, difficulty swallowing, constant vomiting or blood vomiting. In these cases administration of the drug may partially relieve the symptoms and delay the correct diagnosis;
- previous surgical intervention in the gastrointestinal tract or stomach ulcer;
- continuous symptomatic treatment of dyspepsia and heartburn for 4 and more weeks;
- hepatic diseases including jaundice and hepatic failure;
- other serious conditions worsening general health;
- age above 55 years with an onset of new or recent change in existing symptoms.

Patients should not take another proton pump inhibitor or H2 antagonist concomitantly.

Patients should be advised that the tablets are not intended to provide immediate relief.

Patients may start to experience symptomatic relief after approximately one day of treatment with pantoprazole, but it might be necessary to take it for 7 days to achieve complete heartburn control. Patients should not take pantoprazole as a preventive medicinal product.

Administration of drugs reducing gastric acidity leads to an insignificantly increased risk of gastrointestinal infections caused by Salmonella, Campylobacter or C. difficile species.

Proton pump inhibitors are associated with very infrequent cases 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 Controloc®. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

When carrying out laboratory tests, it is necessary to take into account that increased CgA level may interfere with investigations for neuroendocrine tumours. In this regard, the use of the drug Controloc® treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

This medicinal product is intended for short-term use (up to 4 weeks) only.

Patients should be warned about additional risks with long-term use of the medicinal products and the need for prescription and regular surveillance should be emphasized.

The following additional risks are considered relevant for long-term use.

Influence on Vitamin B12 Absorption

Pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with

reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

Bone Fracture

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in older people or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients

at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Hypomagnesemia

Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

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

Effects on ability to drive a car and operate machinery

One should restrain from driving motor vehicles and operating machinery requiring extra attention due to a risk of dizziness and vision disturbances.

Presentation

Tablets gastro-resistant film-coated 20 mg.

14 tablets in Al/Al blister. 1 blister with instructions for medicaluse in a carton pack.

Shelf-life

3 years.

Do not use after the expiry date stated on the package.

Storage conditions

Store at temperature below 25°C.

Keep out of reach of children.

Pharmacy purchasing terms

Without prescription.

Manufacturer/Marketing authorization holder:

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