KLACID® Hp

Product Information

This document refers to the use of pantoprazole, clarithromycin and amoxycillin in combination for the treatment of patients with peptic ulcer disease. The components of this therapy are frequently used to treat other conditions. For information about the treatment of conditions other than peptic ulcer disease, refer to full Product Information for the appropriate component.

Name of Drug

KLACID® Hp is a combination pack containing Klacid® (active ingredient clarithromycin) 500mg tablet, Controloc (active ingredient pantoprazole sodium sesquihydrate 45.1mg which is equivalent to pantoprazole 40mg) 40mg tablet, and Ospamox (active ingredient amoxicillin) 1gm tablet.

Description

KLACID® - pale yellow ovaloid film-coated tablet.
CONTROLOC - yellow, oval, biconvex enteric-coated tablets with a white to off-white core printed with brown ink, on one side: P40.
OSPAMOX - white to cream coloured tablet, oblong, biconvex, with break scores on both sides.

Pharmacology

KLACID® Hp Helicobacter pylori is a spiral, flagellated, Gram-negative rod, primarily colonising the antrum of the stomach, it congregates at, and around intercellular junctions. The natural habitat of H.pylori is the gastric mucosa, where the bacterium attaches itself via adhesion pedestals. H.pylori is associated with duodenal and gastric ulcer disease in about 95% and 70% of patients, respectively. H.pylori is the major factor in the development of gastritis and ulcers in such patients. Eradication of H.pylori is associated with reduced peptic ulcer recurrence. Eradication of H.pylori is therefore appropriate therapy in most patients with duodenal and gastric ulcer where the latter is not caused by non-steriodal anti-inflammatory drug (NSAID) ingestion. Eradication of H.pylori was achieved in approximately 95% of patients following therapy with clarithromycin, pantoprazole and amoxycillin.

KLACID® - Clarithromycin is active in vitro and in vivo against H.pylori. Clarithromycin exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The minimum inhibitory concentrations (MICs) of this metabolite are equal or two- fold higher than the MICs of the parent compound.

CONTROLOC - is an irreversible proton pump inhibitor which has been developed for the treatment of acid-related gastrointestinal disorders. Pantoprazole reduces gastric acid secretion through inhibition of the proton pump on the gastric parietal cell. As a weak base, pantoprazole is highly ionised at low pH and readily accumulates in the highly acidic canalicular lumen of the stimulated parietal cell. In this acidic environment pantoprazole is rapidly converted to the active species, a cationic cyclic sulphonamide, which binds covalently to cysteine residues on the luminal (acidic) surface of H^+, K^+-ATPase to form a mixed disulphide, thereby causing irreversible inhibition of gastric proton pump function. As H^+, K^+-ATPase represents the final step in the secretory process, inhibition of this enzyme suppresses gastric acid secretion regardless of the primary stimulus.
During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumors. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

OSPAMOX - Amoxycillin is a highly potent, broad spectrum penicillin with a particularly rapid onset and a broad spectrum of action (active against both gram-positive and gram-negative micro-organism). Like other penicillins, it acts by inhibiting cell wall synthesis.

Pharmacokinetics

A summary of the pharmacokinetic parameters for KLACID® Hp are provided below. For further information regarding pharmacokinetics of KLACID®, CONTROLOC or OSPAMOX, refer to full Product Information for the appropriate component.

Pharmacokinetic Parameter	KLACID®	CONTROLOC	OSPAMOX
Peak plasma levels	2 hrs	2.7 hrs	1 – 2 hrs
Systemic bioavailability (single dose)	approximately 50%	77%	70-90%
Plasma protein binding	80%	98%	17%
T1/2	5 – 7 hrs	0.9 – 1.9 hrs	1 – 2 hrs
Average peak plasma levels	1.6+0.6mcg/mL (fasting) 2.5+0.8mcg/mL (non-fasting)	2.1 mg/L	30 mg/L

KLACID® - Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of Klacid® tablets. The microbiologically active metabolite 14-hydroxycalrithromycin is formed by first pass metabolism. Klacid® may be given without regard to meals as food does not affect the extent of bioavaibility of Klacid® tablets. Food does slightly delay the onset of absorption of clarithromycin and formation of the 14-hydroxymetabolite. The pharmacokinetics of clarithromycin are non-linear; however, steady-state is attained within 2 days of dosing. At 250mg bid 15-20% of unchanged drug is excreted in the urine. With 500mg bid daily dosing urinary excretion is greater (approximately 36% The 14-hydroxy- clarithromycin is the major urinary metabolite and accounts for 10-15% of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile 5-10% of the parent drug is recovered from the faeces. Klacid® provides tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Klacid® also penetrates the gastric mucus. Levels of

clarithromycin in gastric mucus and gastric tissue are higher when clarithromycin is co-administered with proton pump inhibitor than when clarithromycin is administered alone.

CONTROLOC - Pantoprazole is subjected to low first-pass hepatic extraction, as reflected in an estimated absolute oral bioavailability of 77%. Concomitant intake of food has no influence on the bioavailability of pantoprazole. Plasma pantoprazole concentrations decline monophasically after oral administration, with a mean plasma terminal elimination half-life of 0.9 to 1.9 hours. Despite the short half-life of pantoprazole, inhibition of acid secretion, once accomplished, is long lasting, persisting long after the drug has been cleared from the circulation. On repeated (7 days) oral administration, the pharmacokinetics of pantoprazole (20mg and 40mg/ day) do not differ appreciably from those on single dose administration, suggesting that drug accumulation does not occur. In keeping with its high degree of plasma protein binding (98%), pantoprazole has a relatively low apparent volume of distribution (mean 0.16 L/kg at steady-state), suggesting limited tissue distribution. Pantoprazole is subject to extensive hepatic metabolism via cytochrome P450 (CYP)- mediated oxidation followed by sulphate conjugation. Elimination is renal, with 80% of an oral dose being excreted as urinary metabolites, the remainder is excreted in the faeces and originates primarily from biliary secretion. The pharmacokinetics of pantoprazole do not appear to be modified to any clinically relevant extent by renal impairment. Haemodialysis does not appear to significantly influence the pharmacokinetics of pantoprazole or its main metabolite M2 in patients with renal disease or end stage renal failure. The metabolism of pantoprazole is impaired in patients with hepatic dysfunction. However, Cmax was only marginally elevated (50%), indicating that pantoprazole may be given without dosage adjustment to patients with hepatic impairment.

OSPAMOX - The absorption of amoxycillin is unaffected by meals. The drug is almost completely absorbed from the small intestine. Peak serum levels are reached within 1 to 2 hours after ingestion. Amoxycillin readily distributes in body tissues and fluid including the sputum and purulent bronchial secretions. If liver function is intact, high biliary drug concentrations are reached. Amoxycillin is eliminated at a half-life of approximately 1 to 2 hours. Elimination is predominantly renal. More than half of the oral dose is excreted with the urine in a therapeutically active form.

Indication

Treatment of peptic ulcer disease associated with Helicobacter pylori infection.

Contraindications

KLACID® - is hypersensitivity to macrolide antibiotic drugs or any of the excipients. Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, domperidone, pimozide, terfenadine as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Concomitant administration of clarithromycin and ergot alkaloids (e.g., ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity. Concomitant administration of clarithromycin and oral midazolam is contraindicated. Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes. Clarithromycin should not be given to patients with hypokalemia (risk of prolongation of QT-time).
Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment. Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis. Clarithromycin (and other strong CYP3A4 inhibitors) should not be used concomitantly with colchicine. Concomitant administration with ticagrelor, ivabradine or ranolazine is contraindicated. Concomitant administration of clarithromycin and lomitapide is contraindicated.

CONTROLOC - should not be used in cases of known hypersensitivity to one of the constituents of Controloc or the combination partners. Controloc must not be used in combination treatment for eradication of H.pylori patients with moderate to severe hepatic or renal dysfunction since currently no data are available on the efficacy and safety of Controloc in combination treatment of these patients.

OSPAMOX - known and suspected hypersensitivity to penicillins. Potential cross allergy should be considered in patients with cephalosporin hypersensitivity. Because of the increased incidence of side effects (rashes) amoxycillin should not be administered to patients with mononucleosis and lymphatic leukemia. Severe gastro-intestinal infections with persistent diarrhea or vomiting should not be treated with oral amoxycillin because of the risk of reduced absorption. Special caution should be exercised in patients with allergic diatheses or bronchial asthma and hay fever.

Adverse Reactions

KLACID® - Clarithromycin is generally well tolerated. Side effects reported include nausea, dyspepsia, diarrhoea, vomiting, taste perversion and abdominal pain. Stomatitis, glossitis and oral monilia have been reported. Other side effects include headache and allergic reactions ranging from rash, urticaria and severe cutaneous adverse reactions (SCAR) (e.g. Acute generalized exanthematous pustulosis (AGEP), Steven-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS). There have been reports of transient central nervous system side effects including anxiety, dizziness, insomnia, hallucinations, psychosis, bad dreams and confusion, however, a cause and effect relationship has not been established. There have been reports of hearing loss with clarithromycin which is reversal upon withdrawal of therapy. Pseudomembranous colitis has been reported rarely with clarithromycin, and may range in severity from mild to life threatening. As with other macrolides, hepartic dysfunction (which is usually reversible) including altered liver function tests, hepatitis and cholestasis with or without jaundice, has been reported. Dysfunction may be severe and very rarely fatal hepatic failure has been reported.

CONTROLOC - Treatment with Controloc can occasionally lead to headache, gastrointestinal complaints such as upper abdominal pain, diarrhea, constipation or flatulence and allergic reactions such as pruritus, skin rash (in isolated cases also urticaria or angioedema).

There have been rare reports of nausea, dizziness or disturbances in vision (blurred vision). Peripheral edema, fever, depression or myalgia subsiding after termination of therapy were reported in individual cases.

Microscopic colitis has been included under gastrointestinal disorders with frequency not known while under skin and subcutaneous tissue disorders, there have been report on Stevens-Johnson syndrome; Toxic epidermal necrolysis; Drug reaction with eosinophilia and systemic symptoms; Acute generalized exanthematous pustulosis; Erythema multiforme; Photosensitivity ; Subacute cutaneous lupus erythematosus.

OSPAMOX - Occasional transient side effects are mostly gastro-intestinal (nausea and diarrhea). Owing to the better absorption of amoxycillin they are, however, less commonly seen than during ampicillin treatment. In patients developing diarrhea during treatment pseudomembranous colitis should be considered. (see also 'Special warnings for safe use). Rarely, hypersensitivity reactions like urticarial rashes, fever, joint pain, erythema multiforme, exfoliative dermatitis, angioneurotic edema and hematologic problems, e.g. thrombocytopenia, agranulocytosis, leukopenia and eosinophilia are seen. These usually run a mild course and generally subside within a few days. Like other penicillins, Ospamox may exceptionally cause severe systemic reactions (anaphylactic shock). Exfoliative dermatitis and erytherma multiforme have been described in some cases. Like other penicillins, amoxycillin may cause headache, fatigue, glossitis, stomatitis, fever, joint pain, angioneurotic edema or interstitial nephritis. Minor transient elevations of serum transaminases (SGOT and SGPT) have occasionally been seen.

Precautions/Warnings

KLACID® - The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy. Long-term use may, as with other antibiotics, result in colonization with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted. Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment, colchicine, cardiovascular events, Pneumonia, skin and soft tissue infections of mild to moderate severity, HMG-CoA Reductase Inhibitors (statins), oral hypoglycemic agents/insulin, oral anticoagulants and excipients.
In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR),(e.g Acute generalized exanthematous pustulosis (AGEP). Stevens-Johnson Syndrome, toxic epidermal necrolysis and DRESS); clarithromyhcin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

CONTROLOC - Prior to treatment the possibility of malignancy of gastric ulcer or malignant disease of the esophagus should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant ulcers and can thus delay diagnosis. To date there has been no experience with treatment in children.

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.

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumors. If the patient(s) are due to have a test on CgA level, Controloc treatment should be stopped for at least 5 days before CgA measurements to avoid this interference (see section Pharmacodynamic). 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.

OSPAMOX - Patients should be told about the potential occurrence of allergic reactions and instructed to report them. If allergic reactions occur, the drug should be discontinued and the usual treatment with epinephrine, antihistamines and corticosteroids should be instituted. If maculopapular amoxycillin rashes develop, treatment should be confined to life-threatening conditions and patients should be carefully monitored. Adequate fluid intake and urine output are essential during treatment. Severe and persistent diarrhea should prompt suspicion of antibiotic-induced pseudomembranous colitis (blood-streaked, mucoid, watery diarrhea; dull diffuse or colicky abdominal pain; fever and occasional tenesms), which may be life-threatening. In pertinent cases Ospamox should immediately be withdrawn and treatment specific for the offending organism (e.g. oral Vancomycin) should be instituted. Antiperistaltic drugs are contra-indicated.

Drug Interactions

KLACID® - The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects: Cisapride, domperidone, pimozide, astemizole and terfenadine, ergot alkaloids, oral midazolam, HMG CoA Reductase Inhibitors (statins). Effects of Other Medicinal Products on Clarithromycin: Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine, Etravinine, Fluconazole, Ritonavir. Effect of Clarithromycin on Other Medicinal Products: Antiarrhythmics, Oral hypoglycemic agents/ Insulin, CYP3A-based Interactions, Corticosteroids, Direct acting oral anticoagulants, Omeprazole, Sildenafil, tadalafil, and vardenafil, Theophylline, carbamazepine, Tolterodine, Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam). Other drug interactions: Colchicine, Digoxin, Zidovudine, Phenytoin and valproate. Bi-directional drug interactions: Hydroxychloroquine, Chloroquine, Atazanavir, Calcium channel blockers, Itraconazole, Saquinavir

CONTROLOC - Controloc may reduce the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole). Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. No clinically significant interactions were, however, observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, nifedipine, phenprocoumon, phenytoin, theophylline, warfarin and an oral contraceptive. There werealso nointeractions with concomitantly administered antacids. Human kinetic interaction studies have been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxycillin). No clinically relevant interactions were found.

OSPAMOX - Concomitant ingestion of allopurinol may promote the occurrence of skin rashes. The underlying mechanisms is still poorly understood.As penicillins like amoxycillin only act on proliferating microorganisms, they should not be combined with bacteriostatic antibiotics e.g. tetracyclines and chloramphenicol. If suggested by the outcome of susceptibility tests, combinations with other bactericidal antibiotics (cephalosporins, aminoglycoside) may be used. The concomitant administration of probenecid (e.g. 0.5gm qid orally); contraindicated in children below age 2 years produces sustained and higher plasma level by suppressing renal elimination. Conversely, tissue distribution and diffusion of Ospamox may be reduced by probenecid. Like other antibiotics, aminopenicillin may rarely reduce the efficacy of oral contraceptives. Concomitant antacid intake reduces amoxycillin absorption. Non-enzymatic urinary glucose tests may be false positive. Urobilinogen tests may also be impaired.

Pregnancy and Lactation

KLACID® - The safety of clarithromycin during pregnancy has not been established. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk. The safety of clarithromycin use during breast-feeding of infants has not been established. Clarithromycin is excreted into human breast milk.

CONTROLOC - Clinical experience in pregnant women is limited. There is no information on the excretion of pantoprazole into human breast milk. Controloc tablets should only be used when the benefit to the mother is considered greater than the potential risk to the foetus/baby.

OSPAMOX - There is no current evidence to suggest any embryotoxic, teratogenic or mutagenic effects of Ospamox during pregnancy. It should, however, be borne in mind that amoxycillin diffuses into breast milk.

Dosage and Administration

The recommended dosage regimen for KLACID® Hp is Klacid® 500mg twice daily, Controloc 40mg twice daily and Ospamox 1gm twice daily for 7 days. The combination therapy is implemented for 7 days in general and can be prolonged to up to two weeks maximum.

KLACID® - Klacid may be given without regard to meals as food does not affect the extent of bioavailability.
CONTROLOC - gastro-resistant, tablets should not be chewed or crushed, and should be swallowed whole with water 1 hour before breakfast. In this H.pylori eradication therapy, the second Controloc tablet should be taken before the evening meal.
OSPAMOX - amoxycillin may be given without regard to meals as food does not affect the extent of absorption.

Overdosage

KLACID® - Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalemia and hypoxemia. Allergic reactions accompanying overdosage should be treated by gastric lavage and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

CONTROLOC - There are no known symptoms of overdosage in man. In the case of overdosage with clinical signs of intoxication, the usual rules of intoxication therapy apply.

For full prescribing information, please refer to the individual product pack insert.

Pack Size

KLACID® Hp7 combination pack consists of 14 Klacid® 500mg tablets (blister pack), 14 Controloc 40mg tablets (blister pack) and 14 Ospamox 1gm tablets (blister pack).

KLACID® Hp14 combination pack consists of 28 Klacid® 500mg tablets (blister pack), 28 Controloc 40mg tablets (blister pack) and 28 Ospamox 1gm tablets (blister pack).

Storage condition: Please refer to the individual products.

Shelf life: Please refer to the individual products.

Repacked by
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