CLARITHROMYCIN

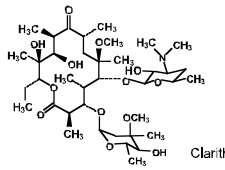
CLARIGET® OD

500mg Extended-Release Tablet

Antibacterial

DESCRIPTION

Clarithromycin is a semi-synthetic macrolide antibiotic obtained by the substitution of the hydroxyl group in position 6 by a CH_3O group in the erythromycin lactonic ring. Chemically clarithromycin is a 6-O-Methyl erythromycin A. The molecular formula is $C_{38}H_{69}NO_{13}$ and the structural formula is



Clarithromycin

FORMULATION

Clarithromcyin (Clariget OD) is available as extended-release film coated tablets as:

Clarithromcyin (Clariget OD) Tablets 500mg
Each extended-release tablet contains:
Clarithromycin USP…500mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Clarithromycin binds to the 50S ribosomal subunit of susceptible microorganisms and inhibits the translocation step, resulting in inhibition of protein synthesis. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two fold lower than the MICs of erythromycin. The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. Clarithromycin is active *in-vitro* against a variety of aerobic and anaerobic gram-positive and gram-negative microorganisms as well as most Mycobacterium avium complex (MAC) microorganisms.

MICROBIOLOGY

Clarithromycin has shown to be active against the following microorganisms:

Aerobic gram-positive microorganisms

Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes
Listeria monocytogenes

Aerobic gram-negative microorganisms

Haemophilus Influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
Legionella spp. (e.g., Legionella pneumophila)

Anaerobes

Clostridium perfringes
Peptococcus species
Peptostreptococcus species
Propionibacterium acnes

Mycobacteria

Mycobacterium leprae
Mycobacterium kansasii
Mycobacterium chelonae
Mycobacterium fortuitum
Mycobacterium avium complex (MAC)
(Consisting of: Mycobacterium avium
Mycobacterium intracellulare)

Other microorganisms

Mycoplasma pneumoniae
Chlamydia pneumonia (TWAR)
Chlamydia trachomatis
Ureaplasma urealyticum

Pharmacokinetics

Absorption:

Clarithromycin extended-release tablets provide extended absorption of clarithromycin from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 50%. Steady state peak plasma concentrations of approximately 1 to 2mcg/mL were achieved about 5 to 6 hours after oral administration of a single 500mg clarithromycin extended-release tablet once daily. For 14-OH clarithromycin, steady state peak plasma concentrations of approximately 0.6mcg/mL were attained about 6 hours after dosing. Little or no unpredicted accumulation was found and the metabolic disposition did not change following multiple dosing.

Effect of Food

The extent of formation of 14-OH clarithromycin following administration of clarithromycin extended-release tablets (2x500mg once daily) is not affected by food, administration under fasting conditions is associated with approximately 30% lower clarithromycin AUC relative to administration with food. Therefore, clarithromycin extended-release tablets should be taken with food.

Distribution:

The drug and its principal metabolite are widely distributed, and tissue concentrations exceed those in serum in part because of intracellular uptake. The protein binding of clarithromycin in human plasma averaged about 70%.

Metabolism and Excretion:

It is extensively metabolized in the liver and undergoes first-pass metabolism.

Elimination half lives of the parent drug and metabolite were approximately 5.3 hours and 7.7 hours respectively. Urinary excretion accounts for approximately 40% of the clarithromycin dose. Fecal elimination accounts for approximately 30%. The apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at higher doses.

Special Populations

Hepatic impairment and Renal insufficiency:

Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.

Geriatric:

Elderly patients with severe renal impairment may require a decrease in dose.

THERAPEUTIC INDICATIONS

Clarithromcyin (Clariget OD) tablets are indicated for the treatment of:

- Lower respiratory tract infections (e.g., bronchitis, pneumonia).
- Upper respiratory tract infections (e.g., pharyngitis, sinusitis, tonsillitis).
- Skin and soft tissue infections (e.g., folliculitis, cellulitis, erysipelas).

DOSAGE AND ADMINISTRATION

Clarithromcyin (Clariget OD) extended-release tablets should be taken with food and should be swallowed whole and not chewed, broken or crushed.

The usual recommended dose of Clarithromcyin (Clariget OD) tablets in adults is 500mg once-daily. In more severe infections, the dosage may be increased to 1000mg once-daily (2x500mg). The usual duration of therapy is 5 to 14 days, excluding treatment of community acquired pneumonia and sinusitis which require 6 to 14 days of therapy.

Renal Impaired Patients

For patients with moderate renal function (creatinine clearance 30-60mL/min), a 50% dosage reduction should be implemented resulting in a maximum dose of one Clarithromcyin (Clariget OD) tablet per day.

CONTRAINDICATIONS

Clarithromycin is contraindicated in:

- Patients with known hypersensitivity to macrolide antibiotic drugs.
- Patients with creatinine clearance less than 30mL/min.
- Concomitant administration with the following medicines:
  - Astemizole
  - Pimozide
  - Cisapride
  - Terfenadine
  - Ergotamine or dihydroergotamine

Clarithromycin in combination with ranitidine bismuth citrate should not be used in patients with a history of acute porphyria.

ADVERSE REACTIONS

Clarithromycin is generally well tolerated.

The most frequently reported side effects of clarithromycin are gastrointestinal related, i.e., nausea, dyspepsia, abdominal pain, vomiting and diarrhea. These are relatively less severe. Other side effects include headache, taste perversion and transient elevations of liver enzymes.

Rashes and Stevens-Johnson syndrome has also been reported. Transient CNS effects include anxiety, dizziness, insomnia, hallucinations and confusion.
Hypoglycemia, thrombocytopenia, interstitial nephtiris, renal failure, hearing loss, glossitis, stomatitis, oral monilla and tongue discoloration, tooth discoloration, hepatitis, hepatic failure, jaundice, electrocardiogram QT prolongation, Torsades de Pointes have also been reported with clarithromycin therapy.

Adverse laboratory changes
Changes in laboratory parameters are:
Hepatic: Elevated SGPT (ALT), SGOT (AST), GGT, alkaline phosphates, LDH, bilirubin.
Hematologic: Decreased WBC, elevated prothrombin time.
Renal: Elevated BUN, elevated serum creatinine.

PRECAUTIONS
- 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.
- Caution should be exercised in administering clarithromycin to patients with impaired hepatic function and to patients with moderate renal function.
- Caution should also be paid to the possibility of cross-resistances between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.
- Pseudomembranous colitis has been reported with nearly all anti-bacterial agents, including clarithromycin, and may range in severity from mild to life threatening. Therefore it is important to consider this diagnosis in patients who have diarrhea subsequent to the administration of antibacterial agents. After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated.
- Safety and effectiveness of clarithromycin in pediatric patients under 6 months of age have not been established.
- It may cause exacerbation of symptoms of myasthenia gravis.

Pregnancy
Clarithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It should not be prescribed particularly during the first 3 months of pregnancy.

Nursing Mothers
The safety of clarithromycin during breast-feeding of infants has not been established. Clarithromycin is excreted into human breast milk.

DRUG INTERACTIONS
As with other macrolide antibiotics the use of clarithromycin in patients concurrently taking drugs metabolised by the cytochrome P450 system (e.g., Cilostazol, methylprednisolone, anticoagulants (e.g., warfarin) quinidine, sildenafil, ergot alkaloids, alprazolam, triazolam, midazolam, disopyramide, lovastatin, rifabutin, phenytoin, cyclosporin, vinblastine, valproate and tacrolimus) may be associated with elevations in serum levels of these other drugs.

Digoxin:
Elevated digoxin serum concentrations have been reported in patients receiving clarithromycin tablets and digoxin concomitantly. Monitoring of serum digoxin levels should be considered.

Quinidine/Disopyramide: There have been post marketed reports of Torsades de Pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiogram and serum levels of these medications should be monitored during clarithromycin therapy.

HMG-CoA reductase Inhibitors:
As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g., statins). Rhabdomyolysis has also been reported in patients taking these drugs concomitantly.

Theophyline, Carbamazepine:
The administration of clarithromycin to patients receiving theophylline or carbamazepine has been associated with an increase in serum theophylline or carbamazepine levels.

Oral Anticoagulants:
Concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of oral anticoagulants. Prothrombin time should be carefully monitored while patients receiving clarithromycin and oral anticoagulants simultaneously.

Ritonavir:
Ritonavir increases the area under the curve (AUC), C_{max} and C_{min} of clarithromycin when administered concurrently. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CL_{CR} 30 to 60mL/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} <30mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1g/day should not be co-administered with ritonavir.

Efavirenz, nevirapine, rifampicin, and rifabutin:
Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin and rifabutin may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Sildenafil, tadalafil and vardenafil:
Each of these phosphodiesterase inhibitors is metabolised, at least in part, by CYP3A and CYP3A may be inhibited by concomitantly administered clarithromycin. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these medicines are co-administered with clarithromycin.

Triazolam:
Medicine interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam have been reported. Monitoring the patient for increased CNS pharmacological effects is suggested.

Colchicine:
When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity.

Itraconazole:
Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacological effect.

Zidovudine:
Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. This interaction does not appear to occur in pediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine.

OVERDOSAGE
Overdosage of clarithromycin can cause gastrointestinal symptoms such as: abdominal pain, vomiting, nausea, and diarrhea. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum concentrations are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

AVAILABILITY
Clarithromycin (Clariget OD) 500mg extended-release tablets are available in blister packs of 5's.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Keep out of reach of children.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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