CLARITEK™

کلیری ٹیک

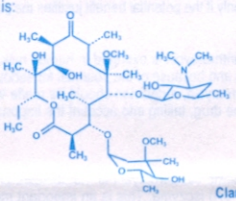
(Clarithromycin)

Tablets / Suspension

250mg, 500mg, 125mg / 5ml

DESCRIPTION

Clarithromycin is a semi-synthetic macrolide antibiotic obtained by substitution of the hydroxyl group in position 6 by a CH_3O group in the erythromycin lactonic ring. Chemically clarithromycin is 6-0-Methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$ and the structural formula is:



Clarithromycin

QUALITATIVE & QUANTITATIVE COMPOSITION

CLARITEK (Clarithromycin) is available as film coated tablets and oral suspension:

1. CLARITEK Tablets 250mg
   Each film-coated tablet contains:
   Clarithromycin USP...250mg

2. CLARITEK Tablets 500mg
   Each film-coated tablet contains:
   Clarithromycin USP...500mg

3. CLARITEK Granules 125mg/5ml (50ml)
   Each reconstituted 5ml contains:
   Clarithromycin USP...125mg

4. CLARITEK Drops 125mg/5ml (25ml)
   Each reconstituted 5ml contains:
   Clarithromycin USP...125mg

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. 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 gonorrheae
Legionella spp. (e.g. Legionella pneumophila)

Mycobacteria
Mycobacterium leprae
Mycobacterium kansasii
Mycobacterium chelonae
Mycobacterium fortuitum
Mycobacterium avium complex [MAC] (consisting of: Mycobacterium avium Mycobacterium intracellulare)

Helicobacter
Helicobacter pylori

Other microorganisms
Mycoplasma pneumoniae
Chlamydia pneumoniae (TWAR)
Chlamydia trachomatis
Ureaplasma urealyticum
Protozoan Toxoplasma gondii

Pharmacokinetics

Absorption:
as a suspension produces a steady-state plasma concentration of about 2µg per ml. The time to peak concentration is about 2-3 hours.
The pharmacokinetics of clarithromycin is non-linear and dose dependent; high doses may produce disproportionate increases in peak concentration of the parent drug, due to saturation of the metabolic pathways.

Effect of Food
Food slightly delays the absorption of clarithromycin but does not affect the extent of bioavailability, therefore it may be given without regard to food.

Distribution:
The drug and its principal metabolite are widely distributed, and tissue concentrations exceed those in serum, in part because of intracellular uptake. Volume of distribution is 243-266 liters. Clarithromycin is 65-75% bound to plasma protein in humans.

Metabolism:
It is extensively metabolized in the liver and undergoes first-pass metabolism via three main pathways: demethylation, hydroxylation and hydrolysis to 8 metabolites. One metabolite 14-hydroxy clarithromycin has in vitro antimicrobial activity comparable to that of clarithromycin.

Excretion
Clarithromycin is excreted in the feces (4%) via the bile. Substantial amounts are excreted in urine; at steady state about 20% and 30% of a 250mg or 500mg dose, respectively, is excreted in this way, as unchanged drug. Approximately 40mg of the dose of 250mg suspension given twice a day is excreted in the urine as the unchanged drug. 14-hydroxy clarithromycin as well as other metabolites are also excreted in the urine accounting for 10 to 15% of the dose. The terminal half-life of clarithromycin is reportedly about 3 to 4 hours in patients receiving 250mg doses twice daily, and about 5 to 7 hours in those receiving 500mg twice daily. The principal metabolite, 14-OH-clarithromycin has an elimination half-life of 5 to 6 hours after a dose of 250mg every 12 hours. While with a dose of 500mg every 12 hours, the elimination half-life is about 7 hours.

Special Populations

Hepatic Impairment:
The principal metabolite 14-OH-clarithromycin concentrations were lower in the hepatically impaired subjects. No dose adjustment is needed.

Renal Insufficiency:
The plasma levels, half-life, Cmax and Cmin for both clarithromycin and its 14-OH metabolite were higher and the AUC was larger in subjects with renal impairment than its normal subjects.

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

Pediatric:
Drug absorption appeared to be rapid following a brief delay in its onset, the mean peak concentrations in plasma (Cmax) for clarithromycin were reached within about 3 hours under both conditions. Data indicate good absorption and no significant effects by food.

THERAPEUTIC INDICATIONS

CLARITEK (Clarithromycin) is indicated for treatment of infections due to susceptible organisms. Such infections include:

- Lower respiratory tract infections (e.g., bronchitis, pneumonia)
- Upper respiratory tract infections (e.g. pharyngitis, sinusitis)
- Acute otitis media in children
- Skin and soft tissue infections (e.g., folliculitis, cellulitis, erysipelas)
- Disseminated or localized mycobacterial infections due to MAC.
- To eradicate Helicobacter pylori in treatment regimens for peptic ulcer disease. It has been tried in protozoal infections, including toxoplasmosis.
- To prevent disseminated Mycobacterium avium complex (MAC) disease in patients with advanced HIV infection.
- As an alternative treatment to penicillins for prophylaxis of endocarditis.

DOSAGE AND ADMINISTRATION

Adults:
The usual recommended dosage of CLARITEK (Clarithromycin) is one 250mg tablet twice daily. In more severe infections the dosage can be increased to 500mg twice daily. The usual duration of therapy is 7 to 14 days. CLARITEK (Clarithromycin) may be taken with or without food.

CLARITEK (Clarithromycin) suspensions may be used as an alternative dosage form for those adults that prefer a liquid medicine.

The following table is a suggested guide for determining dosage:

Adult Dosage Guidelines		
Infection	**Dosage (q12h)**	**Normal Duration (days)**
Pharyngitis/Tonsillitis	250mg	10
Acute maxillary sinusitis	500mg	14
Acute exacerbation of chronic bronchitis due to:		
S. pneumoniae	250mg	7 to 14
M. catarrhalis	250mg	7 to 14

Children: The usual recommended daily dosage of CLARITEK (Clarithromycin) is 7.5mg/kg bid up to a maximum of 500mg twice daily. The usual duration of treatment is for 5 to 10 days depending on the pathogen involved and the severity of the condition.
The following table is a suggested guide for determining dosage.

Pediatric Dosage Guidelines (Based on Body Wt.)		
Weight*	Dosage in mg	Dosage in ml 125mg/5mL
8-11 kg	62.5mg b.i.d	2.5mL (½ tsp. b.i.d.)
12-19 kg	125mg b.i.d	5mL (1 tsp. b.i.d.)
20-29 kg	187.5mg b.i.d	7.5mL (1 ½ tsp. b.i.d.)
30-40 kg	250mg b.i.d	10mL (2 tsp. b.i.d.)
* Children < 8kg should be dosed on a per kg basis (approx 7.5mg/kg BID)		

Dosage for the eradication of H. pylori associated with peptic ulcer disease
CLARITEK (Clarithromycin), usually in a dose of 500mg twice daily, is given with another antibacterial and either a proton pump inhibitor or a histamine H_2-receptor antagonist, for 7 to 14 days.

Dosage for Mycobacterial Infections
Adults: CLARITEK (Clarithromycin) is recommended as the primary agent for the prophylaxis and treatment of disseminated infection due to Mycobacterium avium complex. Clarithromycin should be used in combination with other anti-mycobacterial drugs that have shown in vitro activity against MAC or clinical benefit in MAC treatment. The recommended dose for mycobacterial infections in adults is 500mg bid.

Children: In children, the recommended dose is 7.5mg/kg bid up to 500mg bid. Dosing recommendations for children are in the table above.

Renal Impaired Patients:
In the presence of severe renal impairment (CL_{CR} < 30 ml/min), with or without coexisting hepatic impairment, the dose should be halved or the dosing interval doubled.
In children with creatinine clearance less than 30ml/min, the dosage of clarithromycin should be reduced by one-half, i.e., up to 250mg once daily, or 250mg twice daily in more severe infections. Dosage should not be continued beyond 14 days in these patients.

Directions for Preparing Oral Suspension
Fill previously boiled and cooled water up to the line mark on the bottle and shake vigorously. The reconstituted suspension can be used for up to 14 days, when stored at room temperature. After mixing unlike other suspensions, it should not be refrigerated.

CONTRAINDICATIONS
- Clarithromycin is contraindicated in patients with known hypersensitivity to macrolide antibiotic drugs.
- Concomitant administration of clarithromycin with any of the following medicines is contraindicated: astemizole, cisapride, pimozide and terfenadine.

ADVERSE REACTIONS
Clarithromycin is generally well tolerated. The safety profile of the pediatric formulation is similar to that of the 250mg tablet in adult patients.
The most frequently reported side effects of clarithromycin are gastrointestinal related, i.e. nausea, dyspepsia, abdominal pain, vomiting and diarrhoea. Other reported side effects include headache, taste perversion and transient elevations of liver enzymes.
Headache and rashes from mild skin eruptions to, rarely, Stevens-Johnson syndrome has occurred. There have also been reports of transient CNS effects such as anxiety, dizziness, insomnia, hallucinations, and confusion.

Other adverse effects include hypoglycaemia and thrombocytopenia. Interstitial nephritis, renal failure, hearing loss, glossitis, stomatitis, oral monilia and tongue discoloration have been reported with clarithromycin therapy.

Adverse laboratory changes. Abnormal liver function test results may occur following therapy with clarithromycin. Changes in laboratory parameters without regard to drug relationship are:
Hepatic – elevated SGPT (ALT), SGOT (AST), GGT, alkaline phosphates, LDH, bilirubin.
Hematologic – decreased WBC, platelet count, elevated prothrombin.
Renal - elevated BUN, serum creatinine.

Immunocompromised Paediatric Patients:
In immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it is often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of HIV disease or inter-current illness.
The most frequently reported adverse events, excluding those due to the patient's concurrent condition, were tinnitus, deafness, vomiting, nausea, abdominal pain, purpuric rash, pancreatitis and increased amylase. Evaluations of laboratory values for these patients were made by analyzing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. None of these seriously abnormal values for these laboratory parameters were reported for patients receiving the highest dosage (25mg/kg/day) of clarithromycin.

PRECAUTIONS
- Caution is required in severe renal impaired patients with/without co-existing hepatic impairment.
  Decreased dosage or prolonged dosing intervals may be required.
- 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 macrolides, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents. After the diagnosis of Pseudomembranous colitis has been established, therapeutic measures should be initiated.
- Clarithromycin in combination with ranitidine bismuth citrate therapy should not be used in patients with a history of acute porphyria.

Pregnancy:
There are no adequate or well-controlled studies in pregnant women. Clarithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:
It is not known whether clarithromycin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from clarithromycin, a decision should be made whether, to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Drug interactions:
Data available to date indicate clarithromycin is metabolized primarily by the hepatic cytochrome P450 3A (CYP3A) isozyme. This is an important mechanism determining many drug interactions.
The metabolism of other drugs by this system may be inhibited by concomitant administration with clarithromycin and may be associated with elevations in serum levels of drugs classes known or suspected to be metabolized by the same CYP450 and CYP3A isozyme.

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). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Antiretroviral Drug Interactions:
Zidovudine: Simultaneous oral administration of clarithromycin and zidovudine to adult patients resulted 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.

Ritonavir: Concomitant administration of clarithromycin and ritonavir resulted in a 77% increase in clarithromycin AUC and a 100% decrease in the AUC of 14-OH clarithromycin. Clarithromycin may be administered without dosage adjustment to patients with normal renal function taking ritonavir. 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%.

OVERDOSAGE:
Overdose 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.

HOW SUPPLIED
Claritek (Clarithromycin) Tablets 250mg are available in blister packs of 10's.
Claritek (Clarithromycin) Tablets 500mg are available in blister packs of 10's.
Claritek (Clarithromycin) Granules 125mg/5ml are available in 50ml.
Claritek (Clarithromycin) Drops 125mg/5ml are available in 25ml.

STORAGE
Store below 30°C.
Protect from sunlight and moisture.

Keep out of the reach of children.

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

Manufactured by:
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