

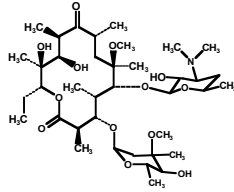
CLARITEK™

(Clarithromycin)

250mg & 500mg Tablets
125mg / 5mL & 250mg / 5mL Suspension

DESCRIPTION

Claritek (Clarithromycin) is a semi-synthetic macrolide antibiotic obtained by substitution of the hydroxyl group in position 6 by a CH₂O group in the erythromycin lactonic ring. Chemically clarithromycin is 6-O-Methylethylerythromycin. The molecular formula is C₃₈H₆₉NO₁₃ and the structural formula is:



Clarithromycin

QUALITATIVE & QUANTITATIVE COMPOSITION

CLARITEK (Clarithromycin) is available for oral administration as:

- CLARITEK Tablets 250mg
Each film-coated tablet contains:
Clarithromycin USP...250mg
- CLARITEK Tablets 500mg
Each film-coated tablet contains:
Clarithromycin USP...500mg
- CLARITEK Granules 125mg/5mL
Each reconstituted 5mL contains:
Clarithromycin USP...125mg
- CLARITEK Drops 125mg/5mL
Each reconstituted 5mL contains:
Clarithromycin USP...125mg
- CLARITEK Dry Suspension 250mg/5mL
Each reconstituted 5mL contains:
Clarithromycin USP...250mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Clarithromycin exerts its anti-bacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms.

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*)

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:

Clarithromycin is rapidly and well absorbed from the gastrointestinal tract but undergoes extensive first-pass metabolism after oral administration. The absolute bioavailability of a 250mg clarithromycin tablet is approximately 50%. The bioavailability of the suspension is identical to or slightly higher than the bioavailability of the tablets. The pharmacokinetic profile of the suspension in

كليري شيك

children corresponds to the pharmacokinetic profile of the suspension in adults. Due to its chemical structure (6-O-Methylethylerythromycin) clarithromycin is quite resistant to degradation by stomach acid. After oral administration of 250mg & 500mg clarithromycin twice daily, peak plasma levels of 1-2 µg/mL & 2.8µg/mL were observed respectively in adults. The peak plasma concentration of pharmacological active 14-hydroxy metabolite was 0.6µg/mL after the administration of 250mg clarithromycin twice daily. Steady state is attained within 2 days of dosing.

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:

Clarithromycin penetrates well into different compartments, with an estimated volume of distribution of 200-400L. Clarithromycin provides concentrations in some tissues that are several times higher than the circulating level of the active substance. Increased levels have been found in both tonsils and lung tissue. Clarithromycin also penetrates the gastric mucus. Clarithromycin is approximately 80% bound to plasma proteins at therapeutic levels.

Metabolism:

Clarithromycin is rapidly and extensively metabolised in the liver. Metabolism involves mainly N-dealkylation, oxidation and stereospecific hydroxylation at position C14.

Excretion

Clarithromycin is excreted in the feces (5-10%) via the bile. At steady state approximately 20% and 30% of clarithromycin is excreted as unchanged drug in urine. 14-hydroxy clarithromycin as well as other metabolites are also excreted in the urine accounting for 10% to 15% of the dose. The elimination 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 twice daily and about 7 to 9 hours in those receiving 500mg twice daily.

Special Populations

Renal impairment:

The plasma levels, half-life, C_{max} and C_{min} for both clarithromycin and its 14-OH metabolite were higher and the AUC was larger in subjects with renal impairment.

Geriatric:

Elderly patients with severe renal impairment may require dose adjustment.

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, tonsillitis)
- Acute otitis media in children
- Skin and soft tissue infections (e.g., folliculitis, cellulitis, erysipelas, impetigo, abscesses)
- Disseminated or localized mycobacterial infections due to MAC.
- To eradicate *Helicobacter pylori* in treatment regimens for peptic ulcer disease.
- To prevent disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection.
- As an alternative treatment to penicillins for prophylaxis of endocarditis.

DOSE AND ADMINISTRATION

Adults:

The usual recommended dosage of CLARITEK (Clarithromycin) is 250mg tablet twice daily. In more severe infections the dosage can be increased to 500mg twice daily. The usual duration of therapy is 6 to 14 days.

The following table is a suggested guide for determining dosage:

ADULT DOSAGE GUIDELINES		
Infection	Dosage (q12h)	Normal Duration (Days)
Pharyngitis/Tonsillitis due to		
<i>S. pyogenes</i>	250mg	10
Acute maxillary sinusitis due to		
<i>H. influenzae</i>	500mg	14
<i>M. catarrhalis</i>	500mg	14
<i>S. pneumoniae</i>	500mg	14
Acute exacerbation of chronic bronchitis due to		
<i>H. influenzae</i>	500mg	7-14
<i>H. parainfluenzae</i>	500mg	7
<i>M. catarrhalis</i>	250mg	7-14
<i>S. pneumoniae</i>	250mg	7-14
Community-Acquired pneumonia due to		
<i>H. influenzae</i>	250mg	7
<i>H. parainfluenzae</i>	-	-
<i>M. catarrhalis</i>	-	-
<i>S. pneumoniae</i>	250mg	7-14
<i>C. pneumoniae</i>	250mg	7-14
<i>M. pneumoniae</i>	250mg	7-14
Uncomplicated skin and skin structure		
<i>S. aureus</i>	250mg	7-14
<i>S. pyogenes</i>	250mg	7-14

Children: The usual recommended daily dosage of CLARITEK (Clarithromycin) suspension is 7.5mg/kg B.I.D up to a maximum of 500mg twice daily. The usual duration of treatment is 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	Dosage in mL 250mg/5mL
8-11 kg	62.5mg b.i.d	2.5mL b.i.d	1.25 mL b.i.d
12-18 kg	125mg b.i.d	5mL b.i.d	2.5mL b.i.d
20-28 kg	187.5mg b.i.d	7.5mL b.i.d	3.75mL b.i.d
30-40 kg	250mg b.i.d	10mL b.i.d	5mL b.i.d

*Children <6kg should be dosed on a per kg basis (approx 7.5mg/kg B.I.D)

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 H₂-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 antimycobacterial 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 b.i.d.

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

Renal Impaired Patients:

The maximum recommended dosages should be reduced proportionately to renal impairment. At creatinine clearance rate of < 30 mL/min, the dosage should be halved to 250mg daily or in the most severe infections to 250mg twice daily for adults and 7.5 mg/kg once a day for children. The duration of treatment should not exceed 14 days in these patients.

Direction for reconstitution

Fill previously boiled and cooled water up to the mark on the bottle and shake well. After mixing, do not refrigerate. Keep tightly closed after use.

CONTRAINDICATIONS

- Clarithromycin is contraindicated in patients with known hypersensitivity to the active substance, other macrolide antibiotics or to any of the excipients.
- Concomitant administration of clarithromycin with any of the following medicines is contraindicated: astemizole, cisapride, pimozone and terfenadine.
- Concomitant administration of Clarithromycin with ergot derivatives is contraindicated.

ADVERSE REACTIONS

The following side effects were reported with the use of Clarithromycin:
Common: Oral monilia, headache, smell alteration, nausea, diarrhea, vomiting, abdominal pain, dyspepsia, stomatitis, glossitis, reversible tooth and tongue discoloration, and taste perversion, i.e. metallic or bitter taste.
Uncommon: Decreased leucocyte levels, allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis, hepatic dysfunction which is usually transient and reversible, hepatitis and cholestasis with or without jaundice, arthralgia and myalgia.
Rare: Tinnitus

Very Rare: Thrombocytopenia, anxiety, insomnia, hallucinations, psychosis, disorientation, depersonalisation, bad dreams and confusion, dizziness, vertigo, paraesthesia, convulsions, Reversible hearing loss, QT prolongation, ventricular tachycardia and Torsades de Pointes, pancreatitis, pseudomembranous colitis in range of severity from mild to life threatening, fatal hepatic failure in patients with pre-existing liver disease or taking other hepatotoxic medicinal products, Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis and renal failure.

PRECAUTIONS

- Caution should be taken in administering Clarithromycin to patients with impaired hepatic function.
- Caution should also be paid to the possibility of cross-resistances between Clarithromycin and other macrolide drugs, as well as lincosamin and clindamycin.
- Pseudomembranous colitis has been reported with the use of broad-spectrum antibiotics. Therefore, it is important to consider its diagnosis in patients who develop severe diarrhea during or after therapy with Clarithromycin.
- Prolonged or repeated use of Clarithromycin may result in superinfections with unsusceptible organisms. In case of superinfection, Clarithromycin therapy should be stopped.
- Clarithromycin should be used with caution whenever indicated for use in patients receiving treatment with an inducer of CYP3A4.
- Clarithromycin in combination with ranitidine bismuth citrate therapy should not be used in patients with a history of acute porphyria.
- Clarithromycin, is an inhibitor of the metabolising enzyme CYP3A4 should not be used concomitantly with different CYP3A4 substrates unless plasma levels, therapeutic effect or adverse events of the CYP3A4 substrate are closely monitored.

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:

Clarithromycin and its active metabolite are excreted in breast milk. Therefore, diarrhea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be born in mind. The benefit of treatment of the mother should be weighed against the potential risk for the infant.

Drug interactions

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

Quinidine/D isopyramide: Concurrent use of clarithromycin and quinidine or disopyramide may cause Torsades de Pointes. 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.

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 didoxyinosine.

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, dosage adjustments should be considered.

OVERDOSAGE:

Overdose of clarithromycin can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea. Adverse reactions accompanying overdose 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 pack of 10's. Claritek (Clarithromycin) Tablets 500mg are available in blister pack of 10's. Claritek (Clarithromycin) Granules 125mg/5mL are available in 50mL. Claritek (Clarithromycin) Drops 125mg/5mL are available in 25mL. Claritek (Clarithromycin) Dry Suspension 250mg/5mL are available in 70mL.

STORAGE

Store below 30°C.
Protect from sunlight & moisture.
The reconstituted suspension can be used for up to 14 days, when stored at room temperature.

The expiration date refers to the product correctly stored at the required conditions.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

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

Manufactured by:

 **Getz**
pharma
(PVT) LIMITED | 29-30/27,
www.getzpharma.com | K.I.A., Karachi,
Pakistan

L02-200007164