IBCLAR

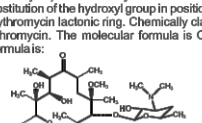
(Clarithromycin) (USP)

آئی بی ۔ کلار
(کلیرتھروومائیسین) یوایس پی

125mg/5ml Dry Suspension

DESCRIPTION

IBCLAR (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-O-Methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$ and the structural formula is:



Clarithromycin

QUALITATIVE & QUANTITATIVE COMPOSITION

IBCLAR (Clarithromycin) is available for oral administration as:

IBCLAR Dry Suspension
Each 5ml contains:
Clarithromycin USP 125mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Clarithromycin exerts its anti-bacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and s uppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gramnegative 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 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:
Clarithromycin is rapidly and well absorbed from the gastrointestinal tract but undergoes extensive first-pass metabolism after oral administration. The absolutebioavailabl lity of a 250mg clarithromycin tablet is approximately 50%. The bioavailab ility of the suspension is identi cal to or slightly higher than the bioavailability of the tablets. The pharmac okinetic profile of the suspension in children corresponds to the pharmacokinetic profile of the suspension in adults.Due to its chemical structure (6-O-Methylerythromycin) 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 ofpharmacological 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 tis sue. Clarithromycin also penetrates the gastric mucus.
Clarithromycin is approximately 80% bound to plasma proteins at therapeutic levels.

Metabolism:
Clarithromycin is rapidly and ex tensively 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 6hours 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_{ss} 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

IBCLAR (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.

DOSAGE AND ADMINISTRATION

Adults:
The usual recomended dosage of IBCLAR (Clarithromycin) is 250mg 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	Doasge (q12h)	Normal Duration (Days)
Pharyngitis/Tonsillitis due to		
s. pyogenes	250mg	10
Acute maxillary sinusitis due to		
H. influenzae	500mg	14
M. catarrhalis	500mg	14
S. pneumonae	500mg	14
Acute exacerbation of chronic bronchitis to		
H. influenzae	500mg	7-14
H. parainfluenzae	500mg	7
M. catarrhalis	250mg	7-14
s. pneumoniae	250mg	7-14
Community-Acquired pneumonia due to		
H. influenzae	250mg	7
H. parainfluenzae	-	-
M. caterrhalis	-	-
S. pneumoniae	250mg	7-14
C. pneumoniae	250mg	7-14
M. pneumoniae	250mg	7-14
Uncomplicated skin and skin structure		
S.aureus	250mg	7-14
S. pyogenes	250mg	7-14

Children: The usual recommended daily dosage of IBCLAR (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
8-11kg	52.5mg b.i.d	2.5mL b.i.d
12-19 kg	125mg b.i.d	5mL b.i.d
20-29 kg	7.5mL b.i.d	7.5mL b.i.d
30-40kg	10mL b.i.d	10mL b.i.d

* Children <8kg 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 IBCLAR (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: IBCLAR (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, pimozide 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 anaphylax is, hepatic dysfunction which is usually transient and reversible, hepatitis and cholestasis with or without jaundic e, arthralgia and myalgia.

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 Clarithrom ycin 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 lincomycin 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 Clarit hromycin may result in superinfections with insusceptible 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.

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 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, dosage adjustments should be considered.

OVERDOSAGE:

Overdose of clarithromycin can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea. Adverse reactions accompanying overdosage s hould be treated by the prom pt elimination of unabsorbed drug and support ive measures. As with other macrolides , clarithromycin serum concentrations are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

HOW SUPPLIED

IBCLAR (Clarithromycin) 125mg/5ml Dry Suspension is available in 60ml when reconsituted.

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 c ontinually updated from time to time.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں یا تفصیلی ہدایات کیلئے ڈبے کے اندر موجود پرچہ ملاحظہ کریں۔
ہدایات: دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔

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