LARICID

Tablets & Suspension

Composition

Laricid 500 Tablets
Each film coated tablet contains Clarithromycin 500 mg

Laricid Suspension 250 mg/5 ml
Each 5 ml of constituted suspension contains Clarithromycin 250 mg

Action

Clarithromycin is a macrolide antibiotic. It exerts its antibacterial action by binding reversibly to the 50S ribosomal subunit of the 70S ribosome of sensitive microorganisms, thereby inhibiting bacterial RNA-dependant protein synthesis. The *in vitro* (*in vitro* sensitivity does not necessarily imply *in vivo* efficacy) antibacterial spectrum of pathogens sensitive to clarithromycin includes:

Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus pneumoniae, Legionelle pneumophilia , Mycoplasma pneumoniae, Chlamydia trachomatis, Moraxella (Branhamella) catarrhalis, Haemophilus influenza, Staphylococcus pylori, Mycobacterium avium, Mycobacterium kansasii, Mycobacterium chelonae, Mycobacterium intracellulare

Pharmacokinetics
Clarithromycin is absorbed rapidly from the gastro-intestinal tract after oral administration, but its bioavailability is reduced to 50% to 55% because of rapid first-pass metabolism. Peak plasma concentration occurs approximately 2 hours after administration. Clarithromycin may be given with or without food. Clarithromycin is metabolised by the liver to the active metabolite, 14-hydroxyclarithromycin, as well as to several other metabolites. Both clarithromycin and 14-hydroxyclarithromycin distribute widely throughout the body and achieve high intracellular concentrations.

Clarithromycin does not achieve significant levels in the cerebrospinal fluid. Protein binding of clarithromycin ranges from 40 to 70% and is concentration-dependent. The elimination half-lives of clarithromycin and 14-hydroxyclarithromycin are approximately 3 to 7 and 5 to 9 hours respectively. Longer half-lives observed after larger doses.

Renal and non-renal routes eliminate Clarithromycin. The amount of clarithromycin excreted unchanged in the urine ranges from 20 to 40%, depending on the dose administered and the formulation. Between 10 and 15% of the dose is excreted in the urine as the 14-hydroxy metabolite. Although the pharmacokinetics of clarithromycin are altered in patients with hepatic or renal dysfunction, dosage adjustment is not necessary unless a patient has severe renal dysfunction (creatinine clearance of <30 ml/minute). At higher doses in HIV-infected patients' clarithromycin and 14-hydroxyclarithromycin, concentrations are much higher when compared with usual doses in non-infected patients. The elimination half-lives also appear to lengthen.

Indications

Laricid is indicated for the treatment of the following mild to moderate severe infections caused by susceptible organisms:

- Lower respiratory tract infections such as bronchitis and pneumonia.
- Upper respiratory tract infections such as pharyngitis and sinusitis.
- Mild to moderately severe acute otitis media due to *S. pneumoniae, M. catarrhalis* and *H. influenza.*
- Skin and soft tissue infections such as folliculitis, cellulitis or erysipelas.
- Eradication of *Helicobacter pylori* when used in combination with a proton pump inhibitor and another antibiotic to decrease recurrence of duodenal ulcer.
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Contraindications

- Hypersensitivity to macrolide antibiotics or to any component of the formulation.
- Concomitant administration of Clarithromycin with astemizole, cisapride, pimozide and terfenadine
- Porphyria.

Warnings

Clarithromycin should be used with caution in:

- Liver function impairment –The pharmacokinetics are altered. No dosage adjustment is required in patients with hepatic function impairment, unless there is also concurrent severe renal function impairment.
- Renal function impairment (severe) –The elimination of Clarithromycin is reduced in patients with renal function impairment, especially those with a creatinine clearance of <30 ml/min. The dose of Clarithromycin should be halved or the dosing interval doubled in patients with a creatinine clearance of <30 ml/min.
- Rhabdomyolysis has been reported with concomitant use of Clarithromycin and the HMGCoA reductase inhibitors e.g. simvastatin.
- Rifabutin and rifampicin –May decrease serum concentration of Clarithromycin by >50%. Co-administration has been reported to cause a higher incidence of uveitis compared to rifabutin alone.
- Theophylline –The area under the plasma concentration-time curve is increased. Monitoring of theophylline serum concentrations is recommended.
- Cross-resistance between Clarithromycin and other macrolides, lincomycin and clindamycin have been reported.

Adverse Reactions

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and frequency (wherever applicable). Frequencies are defined as very common (>1/10), common (frequent) (>1/100, <1/10), uncommon (infrequent) (>1/1000, <1/100), rare (>1/10000, <1/1000), very rare (<1/10000) or isolated case reports.

Hematological
Less frequent: Leucopenia, thrombocytopenia.

Endocrine/Metabolic
Less frequent: Hypoglycemia.

Nervous System
Headache, anxiety, dizziness, insomnia, hallucinations, bad dreams, vertigo, tinnitus, disorientation, depersonalization, confusion, hearing loss, convulsions.

Cardiovascular
QT prolongation, ventricular tachycardia, torsades de pointes.

Gastro-intestinal
Frequent: Nausea, vomiting, abdominal pain, abnormal taste, diarrhoea.
Less frequent: Glossitis, stomtatitis, oral candidiasis, tongue discoloration, tooth discoloration, pseudomembranous colitis (abdominal cramps or pain, tenderness, severe, watery diarrhoea that may also be bloody, fever).

Liver
Less frequent: Increase in liver enzymes, hepatocellular and/or cholestatic hepatitis (with or without jaundice), pancreatitis

Skin
Mild skin eruptions, urticaria, Steven's-Johnson syndrome, and toxic epidermal necrolysis.

Other
Allergic reactions, anaphylaxis.

Adverse effects in immunocompromised patients treated with higher doses of Clarithromycin over long periods include nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, hearing disturbance, AST and ALT elevations, elevated BUN levels, abnormally low white blood cell, and platelet counts. Additional low-frequency events included dyspnoea, insomnia, and dry mouth.

Precautions
Treatment with Clarithromycin should be discontinued if any signs of hepatic dysfunction develop. Hepatic dysfunction is usually reversible, but may be severe. In rare instances, hepatic failure with fatal outcome has been reported, usually associated with other serious underlying diseases and/or concomitant medicines.
There have been less frequent reports of hypoglycemia, some of which occurred in patients on concomitant oral hypoglycemics or insulin.

Pregnancy
Category C
Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Nursing mothers
Safety and efficacy in lactation has not been established. Clarithromycin is excreted in the breast milk.

Drug Interactions
Concomitant use of Clarithromycin with:
Astemizole, cisapride, pimozide and terfenadine
Has resulted in cardiac arrhythmias, including QTc-interval prolongation, ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation, and torsade de pointes. Fatalities have occurred. The most likely cause is the inhibition of metabolism of these medicines by Clarithromycin. Concurrent use is contra-indicated.

Anticoagulants such as warfarin
Clarithromycin may result in the potentiation of the effects of warfarin. Prothrombin time should be monitored closely.

Digoxin
Clarithromycin has been shown to increase serum digoxin concentrations. Monitoring of digoxin serum concentrations is recommended.

Carbamazepine or other medicines metabolised by the cytochrome P450 enzyme system for example, alprazolam, cyclosporine, disopyramide, ergot alkaloids, methylprednisolone, midazolam, omeprazole, quinidine, sildenafil,
simvastatin, tacrolimus, triazolam, vinblastine, phenytoin, and valproate
Clarithromycin may be associated with increased levels of these medicines. Serum concentrations of these medicines may require monitoring. Rhabdomyolysis has been reported with concomitant use of Clarithromycin and the HMGCoA reductase inhibitors e.g. simvastatin.

Rifabutin and rifampicin
May decrease serum concentration of Clarithromycin by >50%. Co-administration has been reported to cause a higher incidence of uveitis compared to rifabutin alone.

Dosage and Administration

Children

Safety and efficacy in infants under 6 months of age has not been established. The recommended dose for children under 6 months is based upon a 7,5 mg/kg dose administered twice daily. See dosage table below.

The usual duration of treatment is 5 to 10 days, depending on the pathogen involved and the severity of infection.

In patients with severe renal function impairment (creatinine clearance <30 ml/min), the dosage of Laricid should be reduced by half. Do not continue treatment in these patients for more than 14 days.

Laricid may be taken with or without meals and can be taken with milk.

Weight	Approximate age	Dose in ml of 125 mg/5 ml suspension	Dose in ml of 250 mg/5 ml suspension
8 to 11 kg	1 to 2 years	2,5 ml twice daily	-
12 to 19 kg	2 to 4 years	5 ml twice daily	2,5 ml twice daily
20 to 29 kg	4 to 8 years	7,5 ml twice daily	3,75 ml twice daily
30 to 40 kg	8 to 12 years	10 ml twice daily	5 ml twice daily

Adults

250 mg twice daily.

In more severe infections, the dosage may be increased to 500 mg twice daily.

Renal impairment

Creatinine clearance (<30 ml/min): Reduce dose by half i.e. 250 mg once daily or 250 mg twice daily for severe infections. Limit the duration of treatment to 14 days.

Eradication of *H. pylori*

Adults

500 mg twice daily, in combination with an appropriate antibiotic and an acid lowering agent, for 7 to 10 days.

The safety and efficacy of Clarithromycin in combination with proton-pump inhibitors other than Mepral (omeprazole) has not been established.

Atypical mycobacterial infections (MAC) in HIV patients

Adults

500 mg twice daily

Treatment of disseminated MAC infections in AIDS patients should continue as long as clinical and microbiological benefit is demonstrated. A decrease in efficacy has been noted in patients taking Laricid for more than 12 weeks. Laricid should be used in conjunction with other antimycobacterial agents.

Laricid may be taken with or without meals.

Over Dosage

Manifestations

Ingestion of large amounts of Clarithromycin can be expected to produce gastro-intestinal symptoms. Allergic reactions accompanying over dosage should be treated by the prompt elimination of unabsorbed medicine and supportive measures.

Treatment

Treatment is symptomatic and supportive. Clarithromycin is not expected to be appreciably affected

by hemodialysis or dialysis.

Storage

Store below 25°C.
Keep the bottle tightly closed. **Do not refrigerate or freeze**. Discard the unused portion of constituted suspension after 10 days.
Shake the bottle well before use.
Keep out of reach of children

Presentation

Laricid 500 Tablets
Box of 14 tablets

Laricid Suspension 250
Powder for the preparation of 60 ml suspension