SAME SIZE ARTWORK
LEAFLET SIZE : 176 mm x 186 mm

22 mm

24 mm

SPACE FOR PHARMACODE

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SPACE FOR PHARMACODE

Pneumonia due to Legionella pneumophila	500 to 1000 mg	Depending on patient's response to therapy
Sinusitis	500 mg	14 days
Uncomplicated skin and skin structure infections	250 mg	7 to 14 days

Dosage in Renal Failure
In the presence of severe renal impairment (i.e., creatinine clearance less than 30 milliliters/minute), the dose should be halved or the dosing interval doubled Clarithromycin in combination with ranitidine bismuth citrate therapy is not recommended in patients with creatinine clearance less than 25 milliliters/minute.

Dosage in Hepatic Insufficiency
The dose of Clarithromycin does not need to be adjusted in the presence of hepatic impairment if renal function is normal. The metabolism of Clarithromycin into its 14-hydroxy metabolite was decreased but the renal clearance of Clarithromycin was increased with a net effect of no significant change in the pharmacokinetics of Clarithromycin.

Dosage in Geriatric Patients
Clarithromycin dosage adjustments are not required in healthy elderly patients.

Pediatric Dosage
The safety and efficacy of clarithromycin have not been established in children less than 6 months of age. The safety of clarithromycin has not been studied in Mycobacterium avium complex patients under the age of 20 months. The dosage of clarithromycin tablets in children (over 6 months of age) is as follows:

Indication	Dosage (every 12 hrs)	Duration(days)
Endocarditis prophylaxis	50 mg/kg (single dose)	1 hour before the procedure; do not exceed the adult dosage
Primary Prevention of disseminated mycobacterium avium disease	7.5 mg/ kg (up to 500 mg)	-
Otitis media caused by H.influenzae, M. catarrhalis & S.pneumoniae	7.5 mg/kg	10 days
Pharyngitis and tonsillitis caused by S.pyogenes	7.5 mg/kg	10 days
Pneumonia caused by M.pneumoniae, S.pneumoniae and C.pneumoniae (TWAR)	7.5 mg /kg	10 days
Acute maxillary sinusitis caused by H.influenzae, M.catarrhalis, and S. pneumoniae	7.5 mg /kg	10 days
Skin and skin structure infections caused by S.aureus and S.pyogenes	7.5 mg /kg	10 days

Route of Administration : Oral

SYMPTOMS AND TREATMENT FOR OVERDOSAGE AND ANTIDOTE (S)
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.

PACKING / PACK SIZES
10 Cartons each containing 1 strip of 4 tablets

SHELF LIFE
24 Months

STORAGE CONDITIONS, USER INSTRUCTIONS AND PHARMACEUTICAL PRECAUTIONS
Store below 30°C. Protect from moisture & light.

Maclar 250 mg : MAL06071053AZ

Maclar 500 mg : MAL06071052AZ

Manufactured by:
Glenmark
PHARMACEUTICALS LTD.
Plot No. E-37, 39, MIDC Area, Satpur,
Nasik - 422 007, Maharashtra, India.
℠ Trade Mark

Product Registration Holder:
Glenmark Pharmaceuticals (Malaysia)
Sdn Bhd (660397-W)
D-31-02, Menara Suezcap 1,
No. 2, Jalan Kerinchi,
59200 Kuala Lumpur, Malaysia

PE00000 MY

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Clarithromycin Tablets USP
Maclar® 250/500

COMPOSITION
Each film coated tablet contains:
Clarithromycin USP 500 mg
Excipients q.s.
Colours Quinoline Yellow Lake and Titanium dioxide BP

THERAPEUTIC CLASS
S0700

PHARMACOLOGY
MECHANISM OF ACTION
Clarithromycin is a macrolide antibiotic which binds to the 50S subunit of the bacterial ribosome. By the binding to the ribosome, protein synthesis is inhibited. Clarithromycin is active against a host of aerobic and anaerobic gram-positive and gram-negative bacteria, as well as most Mycobacterium avium complex (MAC) bacteria. The main metabolite of clarithromycin (i.e.14-hydroxyl clarithromycin) is twice as active as clarithromycin against Haemophilus influenzae, but is 4 to 7 times less active than clarithromycin against MAC isolates. The clinical role of the 14-hydroxyl clarithromycin metabolite against susceptible bacteria has not been evaluated.
Chemically, clarithromycin differs from erythromycin only in that it possesses a methoxy group rather than a hydroxyl group at position 6 of the macrolide ring. This not only makes the compound more stable in the presence of gastric acid, but also changes its metabolic fate such that a very active 14-hydroxy-clarithromycin metabolite is formed; this metabolite is more active than the parent compound against Haemophilus influenzae. Clarithromycin is more active than erythromycin against pathogens such as Staphylococcus aureus, Streptococcus pyogenes, and Streptococcus pneumoniae. Clarithromycin accumulates in pulmonary tissue.
At serum concentrations of 2µg/mL, clarithromycin accumulates in leukocytes at concentrations approximately 9 times those reached in the plasma, which makes the drug particularly effective against intracellular pathogens such as Legionella pneumophila and Staphylococcus aureus.

Antimicrobial activity: Clarithromycin is usually active against the following organism in vitro:

Aerobic Gram-positive microorganisms
Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic Gram-negative microorganisms
Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis

Other microorganisms
Mycoplasma pneumoniae
Chlamydia pneumoniae (TWAR)
Legionella pneumophila

Mycobacteria
Mycobacterium avium complex (MAC) consisting of:
Mycobacterium avium
Mycobacterium intracellulare
Beta-lactamase production should have no effect on clarithromycin activity.
NOTE: Most strains of methicillin-resistant staphylococci are resistant to clarithromycin.

Helicobacter
Helicobacter pylori
Omeprazole/clarithromycin dual therapy; ranitidine bismuth citrate/clarithromycin dual therapy; omeprazole /clarithromycin /amoxicillin triple therapy; and lansoprazole / clarithromycin / amoxicillin triple therapy have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections.

PHARMACOKINETICS
Clarithromycin is rapidly absorbed from the gastrointestinal tract following oral administration, and undergoes first-pass metabolism; the bioavailability of the parent drug is about 55%. The extent of absorption is relatively unaffected by the presence of food. Peak concentrations of clarithromycin and its principal active metabolite, 14-hydroxyclarithromycin, are reported to be about 0.9 and 0.6 µg /mL respectively following a single 250-mg dose by mouth; at steady state the same dose given every 12 hours as tablets produces peak concentrations of clarithromycin of about 1 µg/mL.
The pharmacokinetics of clarithromycin is non-linear and dose dependent; high doses may produce disproportionate increases in peak concentrations of the parent drug, due to saturation of the metabolic pathways.

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Clarithromycin and its principal metabolite are widely distributed, and tissue concentrations exceed those in serum, in part because of intracellular uptake. Clarithromycin has been detected in breast milk. It is extensively metabolized in the liver, and excreted in faeces via the bile. At steady state about 20% and 30% of a 250-mg or 500-mg dose as tablets, respectively, is excreted in the urine as unchanged drug. 14-Hydroxyclarithromycin as well as other metabolites is 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 250-mg doses twice daily, and about 5 to 7 hours in those receiving 500 mg twice daily. The half-life is prolonged in renal impairment.

INDICATIONS
Clarithromycin tablets are indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions as listed below:

Adults:
Pharyngitis/Tonsillitis due to *Streptococcus pyogenes*
Acute maxillary sinusitis due to *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae*
Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae*
Community-Acquired Pneumonia due to *Haemophilus influenzae, Mycoplasma pneumoniae, Streptococcus pneumoniae*, Legionella *pneumophila* or *Chlamydia pneumoniae* (TWAR)
Uncomplicated skin and skin structure infections due to *Staphylococcus aureus,* or *Streptococcus pyogenes*
Disseminated mycobacterial infections due to *Mycobacterium avium,* or *Mycobacterium intracellulare*
Eradication of *H. pylori* along with acid suppressants.

CONTRAINDICATIONS
- Hypersensitivity to clarithromycin or other macrolide antibiotics
- Concomitant therapy with cisapride, pimozide, astemizole, or terfenadine; increase risk of cardiac arrhythmias
- Clarithromycin and ergot derivatives should not be co-administered.

SIDE EFFECTS / ADVERSE REACTIONS
Clarithromycin is generally well tolerated. Side effects include nausea, dyspepsia, diarrhoea, vomiting, abdominal pain and paraesthesia. Stomatitis, glossitis, oral monilia and tongue discolouration have been reported. Other side-effects include headache, arthralgia, myalgia and allergic reactions ranging from urticaria, mild skin eruptions and angioedema to anaphylaxis and rarely Stevens-Johnson syndrome / toxic epidermal necrolysis.

Reports of alteration of the sense of smell, usually in conjunction with taste perversion have also been received. There have been reports of tooth discolouration in patients treated with clarithromycin. Tooth discolouration is usually reversible with professional dental cleaning.

There have been reports of transient central nervous system side-effects including dizziness, vertigo, anxiety, insomnia, bad dreams, tinnitus, confusion, disorientation, hallucinations, psychosis and depersonalisation.There have been reports of hearing loss with clarithromycin which is usually reversible on withdrawal of therapy. Pseudomembranous colitis has been reported rarely with clarithromycin, and may range in severity from mild to life threatening.

There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin. There have been very rare reports of uveitis mainly in patients treated with concomitant rifabutin, most of these were reversible. Isolated cases of leukopenia andthrombocytopenia have been reported.

As with other macrolides, hepatic dysfunction (which is usually reversible) including altered liver function tests, hepatitis and cholestasis with or without jaundice, has been reported.

Dysfunction may be severe and very rarely fatal hepatic failure has been reported.

Cases of increased serum creatinine, interstitial nephritis, renal failure, pancreatitis and convulsions have been reported rarely.

As with other macrolides, QT prolongation, ventricular tachycardia and Torsade de Pointes have been rarely reported with clarithromycin.

PRECAUTIONS / WARNINGS
- Monitor prothrombin times when clarithromycin and oral anticoagulants are given simultaneously
- Presence of severe renal impairment (dosage adjustment is needed)
- Concomitant therapy with ranitidine bismuth citrate is not recommended in patients with a history of acute porphyria
- Clarithromycin-resistant strains of Helicobacter pylori are possible; under these conditions do not use regimens that use clarithromycin as the sole antibiotic
- Clarithromycin is principally excreted by the liver and kidney. Caution should be exercised in administering this antibiotic to patients with impaired hepatic or renal function.
- Prolonged or repeated used of clarithromycin may result in an overgrowth of non-susceptible bacteria or fungi. If super-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted.

DRUG INTERACTION
Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range.

Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered.
When clarithromycin and terfenadine were coadministered, plasma concentrations of the active acid metabolite of terfenadine were threefold higher, on average, than the values observed when terfenadine was administered alone. The pharmacokinetics of clarithromycin and the 14-hydroxy-clarithromycin were not significantly affected by coadministration of terfenadine once
clarithromycin reached steady-state conditions. Concomitant administration of clarithromycin with terfenadine is contraindicated.
The steady-state plasma concentrations of omeprazole were increased (C max, AUC 0-24, and t1/2 increases of 30%, 89%, and 34%, respectively); by the concomitant administration of clarithromycin 500 mg administered every 8 hours.
Co-administration of clarithromycin with ranitidine bismuth citrate resulted in increased plasma ranitidine concentrations (57%), increased plasma bismuth trough concentrations (48%), and increased 14-hydroxy-clarithromycin plasma concentrations (31%). However these observations were not clinically significant.
Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients resulted in decreased steady-state zidovudine concentrations.
Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to healthy volunteers led to increases in the mean steady-state clarithromycin Cmin and AUC of 33% and 18%, respectively.
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.
Concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants.
Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post-marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.
Erythromycin and clarithromycin are substrates and inhibitors of the 3A isoform subfamily of the cytochrome P450 enzyme system (CYP3A). Coadministration of erythromycin or clarithromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin or erythromycin.
Drug interactions have been observed with erythromycin products and/or with clarithromycin and the following drugs metabolized by the CYP3A pathway: Antiarrhythmic drugs, ergotamine/dihydroergotamine, benzodiazepines like triazolam, alprazolam and midazolam,
HMG co-enzyme inhibitors like lovastatin and simvastatin, cyclosporine, tacrolimus, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol and bromocriptine.
Concomitant administration of clarithromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated.
There have been reports of interactions of clarithromycin with drugs not thought to be metabolized by CYP3A including hexobarbital, phenytoin, and valproate.

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

Lactation:
It is known that clarithromycin is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk. However, it is not known whether clarithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when clarithromycin is administered to a nursing woman.

RECOMMENDED DOSAGE, DOSAGE SCHEDULE AND ROUTE OF ADMINISTRATION

Indication	Dosage (every 12 hrs)	Duration (days)
Acute exacerbations of Chronic Bronchitis(AECB) due to		
H. influenzae	500 mg	7 to 14
H. parainfluenzae	500 mg	7
M. catarrhalis	250 mg	7 to 14
S. pneumoniae	250 mg	7 to 14
Endocarditis prophylaxis	500 mg	1 hr before procedure
Pharyngitis/tonsillitis caused by S. pyogenes	250 mg	10 days
Pneumonia caused by C. pneumoniae, M catarrhalis, and S. pneumoniae.	250 mg or 500 mg	7 to 14 days 10 days

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