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

CRIXAN

(Clarithromycin for oral suspension USP)

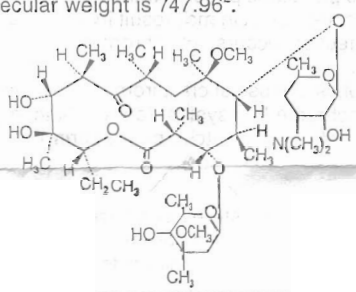
COMPOSITION

CRIXAN Suspension 125 mg
Each 5 ml of the constituted suspension contains :
Clarithromycin USP 125 mg

CRIXAN Suspension 250 mg
Each 5 ml of the constituted suspension contains :
Clarithromycin USP 250 mg

DESCRIPTION

CRIXAN Suspension is an oral formulation of clarithromycin, a semi synthetic macrolide antibiotic. It is chemically designated as 6-0-methyl erythromycin[2]. The molecular formula is $C_{38}H_{69}NO_{13}$ and its molecular weight is 747.96[2].



CLARITHROMYCIN
STRUCTURAL FORMULA

PHARMACOLOGY

Pharmacodynamics

Mode of action[2,3,4]

Clarithromycin exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is active against a wide range of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin. The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity.

Antibacterial Spectrum[2,3,4]

Clarithromycin is usually active against the following organisms *in vitro* :

Gram-positive bacteria	: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes* (Group A β-haemolytic streptococci); α-haemolytic streptococci (viridans group); *Streptococcus (Diplococcus) pneumoniae*; *Streptococcus agalactiae*; *Listeria monocytogenes.*
Gram-negative bacteria	: *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoea, Legionella pneumophila, Bordetella pertussis, Helicobacter pylori.*
Mycoplasma	: *Mycoplasma pneumoniae; Ureaplasma urealyticum.*
Other organisms	: *Chlamydia trachomatis, Mycobacterium avium, Mycobacterium leprae, Mycobacterium fortuitum, Mycobacterium intracellulare, Mycobacterium kansasii*
Anaerobes	: Macrolide-susceptible *Bacteroides fragilis; Clostridium perfringens; Peptococcus* species, *Peptostreptococcus* species; *Propionibacterium acnes.*

PHARMACOKINETICS[2,3]

Clarithromycin is rapidly absorbed from the gastro-intestinal tract following oral administration, and undergoes first pass metabolism; the bioavailability of the parent drug is about 55%. Food does not affect the extent of bioavailability of the drug. Clarithromycin and its 14-OH metabolite distribute readily into body tissues and fluids. Clarithromycin is extensively metabolised in the liver, and excreted in faeces via the bile. Peak serum concentrations are attained within 2 hours of oral dosing, in fasting healthy human subjects. Steady -state peak serum clarithromycin concentrations are attained in 2 to 3 days and are approximately, 3-7 µg/ml in children receiving 7.5 mg/kg (suspension) every 12 hours, and 6-15 µg/ml in children receiving 15 mg/kg (suspension) every 12 hours. The elimination half life ($t_{1/2}$) of clarithromycin is about 3 to 4 hours with 250 mg adminstered every 12 hours but increases to 5 to 7 hours with 500 mg administered every 8 to 12 hours. With a 7.5 mg/kg (suspension) dose every 12 hours in children, the peak steady state concentration of 14 OH clarithromycin is 1 to 2 µg/ml. The plasma protein binding is about 65 to 75%. Approximately 40% of the dose of 250 mg suspension given twice a day is excreted in the urine as clarithromycin.

THERAPEUTIC INDICATIONS[2,3,4,5]

Clarithromycin is indicated in the treatment of infections caused by one or more susceptible organisms. Indications include :

- Upper respiratory tract infections : Simusitis and Pharyngitis
- Lower respiratory tract infections : Pneumonia, Acute and Chronic bronchitis
- Skin and skin structure infections
- Acute otitis media
- Disseminated mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare*

Prophylaxis :

Clarithromycin is indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection.

DOSAGE AND ADMINISTRATION[3,5] **(ORAL)**

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

Paediatric Dosage

The recommended daily dosage in children is based on a 7.5 mg/kg bid regime.
In case of severe infections, the dosage may be increased upto 500 mg b.i.d.

Wt (kg)	Approx.age (yrs)	Dosage (ml) b.i.d.
8-11	1-2	2.5
12-19	3-6	5.0
20-29	7-9	7.5
30-40	10-12	10.0

Children < 8 kg should be given 7.5 mg/kg b.i.d.

Directions for Constitution

Add freshly boiled and cooled water upto the arrow mark on the label. Shake vigorously. Adjust the volume up to the mark by adding more water, if necessary. This makes 60 ml of suspension. The constituted suspension should be used within 14 days.

PRECAUTIONS

General

Clarithromycin is primarily excreted by the liver and kidney. Caution should be exercised in administering clarithromycin to paediatric patients with impaired hepatic and renal function. Prolonged or repeated use 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.

As with other macrolide antibiotics, the use of clarithromycin in patients concomitantly taking drugs metabolised by the cytochrome P_{450} system (eg. warfarin, ergot alkaloids, triazolam, midazolam, disopyramide, lovastatin, phenytoin, cyclosporin) may result in elevations in serum levels of these drugs.

WARNINGS

Monitor ECG if clarithromycin is administered concurrently with cisapride, pimozide or terfenadine since elevated levels of these drugs may occur leading to development of cardiac arrhythmias. Previous history of hypersensitivity to other macrolides should be elicited before prescribing clarithromycin.

CONTRAINDICATIONS[3,4]

Clarithromycin is contraindicated in patients with a previous history of hypersensitivity to clarithromycin or other macrolide antibiotics.Concurrent administration of clarithromycin with ergot derivatives, terfenadine,cisapride or pimozide should be avoided.

USE IN PREGNANCY/LACTATION[3,4]

The safety of clarithromycin during pregnancy and breast feeding of infants has not been established. Clarithromycin should thus not be used during pregnancy or lactation unless the benefit outweighs the risk.

PAEDIATRICS[3]

Appropriate studies on the relationship of age to the effects of clarithromycin have not been performed in children upto 6 months of age. Clarithromycin oral suspension appears to be well tolerated in children 6 months to 12 years of age.

DRUG INTERACTIONS[3,4]

As with other macrolide antibiotics, the use of clarithromycin in patients concomitantly taking drugs metabolised by the cytochrome P450 system (eg. warfarin, ergot alkaloids, triazolam, midazolam, disopyramide, lovastatin, phenytoin, cyclosporin) may result in elevation in serum levels of these drugs. Prothrombin time should be frequently monitored in patients receiving warfarin and clarithromycin concurrently.

Administration of carbamazepine with clarithromycin has been shown to increase significantly, the plasma concentration of carbamazepine; carbamazepine serum levels should be monitored.

Concurrent administration of digoxin with clarithromycin may increase digoxin levels, monitoring of digoxin serum levels is recommended.

Theophylline levels should be monitored in patients who are administered clarithromycin, as increased serum theophylline levels and potential theophylline toxicity may occur during concomitant administration of the two drugs.

Concurrent use of clarithromycin and terfenadine may increase the plasma concentration of terfenadine and its active metabolite by 2 to 3 times; concurrent use should be avoided.

ADVERSE EFFECTS[3,4]

Clarithromycin is generally well tolerated. Side-effects include nausea, vomiting, diarrhoea, abdominal pain, stomatitis and headache. Transient central nervous system side-effects including anxiety, dizziness, insomnia, hallucinations, psychosis and confusion have been reported. Reversible hearing loss, urticaria and mild skin eruptions, anaphylaxis, Stevens-Johnson Syndrome and thrombocytopenia have been known to occur rarely.

Hepatic dysfunction (which is usually reversible) including altered liver function tests, cholestasis with or without jaundice and hepatitis have also been reported. Pseudomembranous colitis may occur with nearly all antibacterial agents including clarithromycin.

OVERDOSE[4]

Ingestion of large amounts of clarithromycin may produce gastro-intestinal symptoms. Overdosage should be treated by gastric lavage and supportive measures.

STORAGE

Store below 25°C, protected from light & moisture.

SUPPLY

CRIXAN SUSPENSION 125 mg : Bottle of 60 ml
CRIXAN SUSPENSION 250 mg : Bottle of 60 ml

Keep all medicines out of the reach of children.

REFERENCES

1. Martindale The Extra Pharmacopoeia 1996; 31st ed; 210-211.
2. Mosby's Gen Rx 1998, 8th ed; II 505-II 511.
3. USPDI Drug Information for the Health Care Professional 1996, 16th ed; 864-867.
4. ABPI Compendium of Data Sheets, 1998-99; 13-15.
5. Physician's Desk Reference 1998; 405-412.

Information compiled in June 2000

MADE IN INDIA

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