CRIXAN OD 500MG TABLETS

(Clarithromycin Extended Release Tablets)

(For oral administration)

COMPOSITION
Active Ingredients
CRIXAN OD 500 mg Tablets
Each film coated tablet contains
Clarithromycin Ph.Eur. 500 mg

Excipients
Hypromellose, Lactose Monohydrate, Microcrystalline Cellulose, Povidone, Colloidal anhydrous silica, Talc, Sodium Stearyl Fumarate, Magnesium Stearate.

Film Coating
Opadry 20H52875 (Yellow), Purified Water

PHARMACEUTICAL FORM AND CONTENTS
Crixan OD 500mg Tablets: Blister strip of 5's. Box of 2x5's

THERAPEUTIC CLASS/ACTIVITY
Antiinfective

Clarithromycin is a semi-synthetic macrolide antibiotic. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis.
Clarithromycin is highly potent against a wide variety 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, formed in man by first pass metabolism, also has antimicrobial activity. The MICs of this metabolite are equal or two-fold higher than the MICs of the parent compound, except for *H. influenzae* where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Clarithromycin is usually active against the following organisms in vitro -
Gram-positive Bacteria: *Staphylococcus aureus* (methicillin susceptible) *Streptococcus pyogenes* (Group A beta-hemolytic streptococci alpha-hemolytic streptococci (viridans group); *Streptococcus (Diplococcus) pneumoniae; Streptococcus agalactiae; Listeria monocytogenes.*
Gram-negative Bacteria: *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae: Legionella pneumophila, Bordetella pertussis, Helicobacter pylori, Campylobacter jejuni.*
Mycoplasma: *Mycoplasma pneumoniae; Ureaplasma urealyticum*
Other Organisms: *Chlamydia trachomatis; Mycobacterium avium, Mycobacterium leprae; Mycobacterium kansasii, Mycobacterium chelonae, Mycobacterium fortuitum; Mycobacterium intracellulare.*
Anaerobes: Macrolide-susceptible *Bacteroides fragilis; Clostridium perfringens;* Peptococcus species; Peptostreptococcus species *Propionibacterium acnes.*
Clarithromycin has bactericidal activity against several bacterial strains. The organisms include *Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae, H. pylori* and Campylobacter spp.

MARKETING AUTHORIZATION HOLDER
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THERAPEUTIC INDICATIONS
CRIXAN (clarithromycin) is indicated for treatment of infections caused by susceptible organisms including:

- Lower respiratory tract infections (acute and chronic bronchitis, and pneumonia).
- Upper respiratory tract infections (sinusitis and pharyngitis)
- Community acquired respiratory infections.
- Skin and soft tissue infections of mild to moderate severity
- Eradication of *H. pylori* in patients with duodenal ulcers (clarithromycin is used in combination with omeprazole or lansoprazole).

CONTRAINDICATIONS
CRIXAN is contraindicated in patients with known hypersensitivity to macrolide antibiotic drugs.
Clarithromycin and erythromycin derivatives should not be coadministered.
Concomitant administration of clarithromycin and any of the following drugs is contraindicated: cisapride, pimozide and terfenadine. Elevated cisapride, pimozide and terfenadine levels have been reported in patients receiving either of these drugs and clarithromycin concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

enzyme system (CYP3A). Coadministration of erythromycin or clarithromycin and a drug primarily metabolized by CYP3A may be associated with elevation in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustment may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving erythromycin or clarithromycin.
The following are examples of some clinically significant CYP3A based drug interactions. Interactions with other drugs metabolized by the CYP3A isoform are also possible. Increased serum concentrations of carbamazepine and the active acid metabolite of terfenadine were observed in clinical trials with clarithromycin.
The following CYP3A based drug interactions have been observed with erythromycin products and/or with clarithromycin in post-marketing experience:
Antiarrhythmics: There have been postmarketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs. Serum concentrations of these medications should also be monitored.
Ergotamine/ Dihydroergotamine: Concurrent use of erythromycin or clarithromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.
Triazolobenzodiazepines (such as triazolam and alprazolam) and related benzodiazepines (such as midazolam): Erythromycin has been reported to decrease the clearance of triazolam and midazolam, and thus, may increase the pharmacologic effect of these benzodiazepines. There have been post-marketing reports of drug interactions and CNS effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam.
HMG-CoA reductase inhibitors. As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.
Sildenafil (Viagra): Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. A similar interaction may occur with clarithromycin. reduction of sildenafil dosage may be considered.
There have been spontaneous or published reports of CYP3A based interactions of erythromycin and/or clarithromycin with carbamazepine, cyclosporine, tacrolimus, alfentanil, disopyramide, quinidine, methylprednisolone, olostazole, bromocriptine and nifedipine.
Concomitant administration of clarithromycin with cisapride, pimozide, astemizole or terfenadine is contraindicated.
In addition there have been reports of interactions of erythromycin or clarithromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin and valproate.

Carcinogenicity/Mutagenicity
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of clarithromycin.
The following *in vitro* mutagenicity tests have been conducted with clarithromycin: Salmonella /Mammalian Microsomes Test, Bacterial Induced Mutation Frequency Test, *In Vitro* Chromosome Aberration Test, Rat Hepatocyte DNA Synthesis Assay, Mouse Lymphoma Assay, Mouse Dominant Lethal Study, Mouse Micronucleus Test. All tests had negative results except the *in vitro* Chromosome Aberration Test which was weakly positive in one test and negative in another. In addition a bacterial reverse-mutation test (Ames Test) has been performed on clarithromycin metabolites with negative results.

Use in Children
See DOSAGE AND ADMINISTRATION.

Use in Pregnancy and Lactation
Clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus. Clarithromycin has demonstrated adverse effects of pregnancy outcome and/or embryo-fetal development in monkeys, rats, mice, and rabbits at doses that produced plasma levels 2 to 17 times the serum levels achieved in humans treated at the maximum recommended human doses.
The safety of clarithromycin during breast feeding of infants has not been established. Clarithromycin should thus not be used during lactation unless the benefits is considered to outweigh the risk. Clarithromycin has been found in the milk of lactating animals and in human breast milk.

Use in Elderly
In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients.

Use in Pathological Conditions
See PRECAUTIONS

Effect on Driving/Machine operating ability
There is no such data available

THIS IS A MEDICAMENT

Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you. Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
The doctor and the pharmacist are the experts in medicines' benefits and risks.
Do not by yourself interrupt the period of treatment prescribed
Do not repeat the same prescription without consulting your doctor.
Keep all medicaments out of reach of children.

Council of Arab Health Ministers.
Union of Arab Pharmacists.

PRECAUTIONS

Prescribing clarithromycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Clarithromycin is principally excreted via the liver and kidney. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.

Clarithromycin in combination with ranitidine bismuth citrate therapy is not recommended in patients with creatinine clearance less than 25 ml/min.

Clarithromycin in combination with ranitidine bismuth citrate should not be used in patients with a history of acute porphyria.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis". After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

WARNINGS

See Pregnancy and Lactation

Drug Interactions

Theophylline: 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. In two studies in which theophylline was administered with clarithromycin (a theophylline sustained-release formulation was dosed at either 6.5 mg/kg or 12 mg/kg together with 250 or 500 mg q12h clarithromycin), the steady-state levels of C_{max}, C_{min}, and the area under the serum concentration time curve (AUC) of theophylline increased about 20%.

Carbamazepine: 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.

Terfenadine: 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 (see CONTRAINDICATIONS).

Omeprazole: Clarithromycin 500 mg every 8 hours was given in combination with omeprazole 40 mg daily to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24h}, and $T_{1/2}$ increases of 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when coadministered with clarithromycin.

Ranitidine: Coadministration 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%). These effects are clinically insignificant.

Zidovudine: Simultaneous oral administration of clarithromycin and zidovudine to HIV-infected adult patients resulted in decreased steady-state zidovudine concentrations. When 500 mg of clarithromycin were administered twice daily, steady-state zidovudine AUC was reduced by a mean of 12%. Individual values ranged from a decrease of 34% to an increase of 14%. Based on limited data in 24 patients, when clarithromycin was administered two to four hours prior to oral zidovudine, the steady-state zidovudine C_{max} was increased by approximately 2-fold, whereas the AUC was unaffected.

Didanosine: Simultaneous administration of clarithromycin and didanosine to 12 HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.

Fluconazole: Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state clarithromycin C_{ss} and AUC of 33% and 18%, respectively. Steady-state concentrations of 14-OH clarithromycin were not significantly affected by concomitant administration of fluconazole.

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, the following dosage adjustments should be considered: For patients with Cl_{cr} 30 to 60 ml/min, the dose of clarithromycin should be reduced by 50%. For patients with Cl_{cr} < 30 ml/min, the dose of clarithromycin should be decreased by 75%.

Oral anticoagulants: Spontaneous reports in the post-marketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously.

Digoxin: 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 levels should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Cytochrome P450 enzyme system: Erythromycin and clarithromycin are substrates and inhibitors of the 3A isoform subfamily of the cytochrome P450

DOSAGE AND ADMINISTRATION

CRIXAN tablets may be given with or without food.

Patients with respiratory tract/skin and soft tissue infections

Adults and Children older than 12 years: The usual dose is 250 mg twice daily for 7 days although this may be increased to 500 mg twice daily for up to 14 days in severe infections.

Eradication of H. pylori in patients with duodenal ulcers (Adults)

Triple Therapy (7 - 14 days)

CRIXAN 500 mg twice daily and lansoprazole 30 mg twice daily should be given with amoxycillin 1000 mg twice daily for 7 - 14 days

Triple Therapy (7 days)

CRIXAN 500 mg twice daily and lansoprazole 30 mg twice daily should be given with metronidazole 400 mg twice daily for 7 days

Or

CRIXAN 500 mg twice daily and omeprazole 40 mg daily should be given with amoxycillin 1000 mg twice daily or metronidazole 400 mg twice daily for 7 days.

Triple Therapy (10 days)

CRIXAN 500 mg twice daily should be given with amoxycillin 1000 mg twice daily and omeprazole 20 mg daily for 10 days

Dual Therapy (14 days)

The usual dose of CRIXAN is 500 mg three times daily for 14 days. Clarithromycin should be administered with oral omeprazole 40 mg once daily. The pivotal study was conducted with omeprazole 40 mg once daily for 28 days. Supportive studies have been conducted with omeprazole 40 mg once daily for 14 days

Renal impairment: Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearance < 30 ml/min). If adjustment is necessary, the total daily dosage should be reduced by half, e.g 250 mg once daily or 250 mg twice daily in more severe infections.

WITHDRAWAL EFFECTS, IF ANY

The termination of treatment with clarithromycin is unlikely to be associated with withdrawal effects.

OVERDOSAGE and its Management

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalemia and hypoxemia. Adverse reactions accompanying overdosage should be treated by gastric lavage and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

Missed dose instructions.

In case a dose is missed, it should be taken as soon as possible unless it is almost time for the next dose. If several doses are missed, the pharmacist/physician must be informed.

ADVERSE REACTIONS

Clarithromycin is generally well tolerated. Side effects include nausea, dyspepsia, diarrhoea, vomiting, abdominal pain and paraesthesia. Stomatitis, glossitis, oral moniliа 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. Isolated cases of leukopenia and thrombocytopenia 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.

Expiry Date with Warning

The product should not be used after the expiry date mentioned on the pack.

STORAGE

Store below 25°C, protected from moisture.

SHELF LIFE

24 Months

Date of Last Revision of Package Leaflet:
November 2004

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

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