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

ACEM™-250 / 500

Clarithromycin Tablets USP

Composition :

ACEM™-250

Each film coated tablet contains :

Clarithromycin USP	250 mg
Excipients	q.s.

ACEM™-500

Each film coated tablet contains :

Clarithromycin USP	500 mg
Excipients	q.s.

DESCRIPTION:

Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-O-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water.

CLINICAL PHARMACOLOGY:

Microbiology

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible bacteria resulting in inhibition of protein synthesis.

Clarithromycin is active in vitro against a variety of aerobic and anaerobic Gram-positive and Gram-negative bacteria as well as mycobacterium avium complex (MAC) bacteria.

Additionally, the 14-OH clarithromycin metabolite also has clinically significant antimicrobial activity. The 14-OH clarithromycin is twice as active against *Haemophilus influenzae* microorganisms as the parent compound. However, for *Mycobacterium avium* complex (MAC) isolates the 14-OH metabolite is 4 to 7 times less active than clarithromycin. The clinical significance of this activity against *Mycobacterium avium* complex is unknown.

Clarithromycin is usually active against following micro-organisms in vitro :

Gram-positive microorganisms

Staphylococcus aureus (methicillin susceptible), *Streptococcus pyogenes*, *Streptococcus pyogenes*, alpha-haemolytic streptococci (viridans group), *Streptococcus agalactiae*, *Listeria ainocytogenes*

Gram-negative microorganisms

Haemophilus influenzae, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, *Legionella pneumophila*, *Bordetella pertussis*, *Helicobacter pylori*, *Campylobacter jejuni*.

Other microorganisms

Mycoplasma pneumoniae, *Ureaplasma urealyticum*, *Chlamydia trachomatis*, *Mycobacterium avium*, *Mycobacterium hanse*, *Mycobacterium intracellulare*

Mycoplasma

Mycoplasma pneumoniae; *Ureaplasma urealyticum*.

Anaerobes

Macrolide-susceptible *Bacteroides fragilis*, *Clostridium perfringens*; *Peptococcus* species, *Peptostreptococcus* species, *Propionibacterium* species.

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* sp.

Pharmacokinetics

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. For a single 500 mg dose of clarithromycin, food slightly delays the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 3.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH clarithromycin or its peak plasma concentration but does slightly decrease the extent of metabolic formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, clarithromycin tablets may be given without regard to food.

Clarithromycin and the 14-OH clarithromycin metabolite distribute readily into tissues and fluids. There are no data available on cerebrospinal fluid penetration. Because of high intracellular concentrations, tissue concentrations are higher than serum concentrations.

In non-fasting healthy human subjects (males and females), peak plasma concentrations were attained within 2 to 3 hours after oral dosing. Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 1 to 2 mcg/mL with a 250 mg dose administered every 12 hours and 3 to 4 mcg/mL with a 500 mg dose administered every 8 to 12 hours. The elimination half-life of clarithromycin was about 3 to 4 hours with 250 mg administered every 12 hours but increased to 5 to 7 hours with 500 mg administered every 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 8 to 12 hours. With a 250 mg every 12 hours dosing, the principal metabolite, 14-OH clarithromycin, attains a peak steady-state concentration of about 0.6 mcg/mL and has an elimination half-life of 6 to 9 hours. With a 500 mg every 8 to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is slightly higher (up to 1 mcg/mL), and its elimination half-life is about 7 to 9 hours. With any of these dosing regimens, the steady-state concentration of this metabolite is generally attained within 3 to 4 days.

After a 250 mg tablet every 12 hours, approximately 20% of the dose is excreted in the urine as clarithromycin, while after a 500 mg tablet every 12 hours, the urinary excretion of clarithromycin is somewhat greater, approximately 30%. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10% to 15% of the dose with either a 250 mg or a 500 mg tablet administered every 12 hours.

INDICATIONS:

Clarithromycin tablets are indicated in adults and adolescents 12 years and older for the treatment of the following bacterial infections, when caused by clarithromycin-susceptible bacteria.

- Lower respiratory tract infections (for example, acute bronchitis and chronic bronchitis, and pneumonia).
- Upper respiratory tract infections (for example, sinusitis and pharyngitis).
- Clarithromycin is appropriate for initial therapy in community acquired respiratory infections and has been shown to be active in vitro against common and atypical respiratory pathogens isolated in the respiratory tract.
- Clarithromycin has also indicated in skin and soft tissue infections of mild to moderate severity.
- Disseminated mycobacterial infections due to *Mycobacterium avium*, or *Mycobacterium intracellulare*.
- Clarithromycin in the presence of acid suppression effected by omeprazole or lansoprazole is also indicated for the eradication of *H. pylori* in patients with duodenal ulcers.

DOSAGE AND ADMINISTRATION:

The dosage of clarithromycin tablets depends on the type and severity of the infection and has to be defined in any case by the physician.

Respiratory tract/skin and soft tissue infection (adults and adolescents (12 years and older)):

- Standard dosage: The usual dose is 250 mg twice daily (in the morning and in the evening).
- High dosage treatment (severe infections): The usual dose may be increased to 500 mg twice daily in severe infections.

The usual duration of therapy is 6-14 days.

Eradication of Helicobacter pylori in patients with duodenal ulcer (adults):

The usual duration of therapy is 6-14 days.

Following triple-drug therapy can be utilized:

- Clarithromycin 500 mg twice daily + lansoprazole 30 mg twice daily or pantoprazole 40 mg daily + amoxycillin 1000 mg twice daily or metronidazole 400 mg twice daily
- Clarithromycin 500 mg twice daily + omeprazole 20 mg daily + amoxycillin 1000 mg twice daily
- Clarithromycin 500 mg twice daily + omeprazole 40 mg daily for 14 days.

Mycobacterial infections (adults):

The recommended dose of clarithromycin for the prevention and treatment of disseminated Mycobacterium avium disease is 500 mg twice daily.

Clarithromycin therapy should continue if clinical response is observed. Clarithromycin can be discontinued when the patient is considered at low risk of disseminated infection.

Dosage in renal impairment:

Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearance <30 mL/min (~0.5 mL/s)). If adjustment of dose is necessary, the total daily dosage should be reduced by half.

The duration of treatment should not exceed 14 days in these patients.

Method of administration:

The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water).

Clarithromycin may be given irrespective of food intake.

CONTRAINDICATIONS:

- Clarithromycin is contraindicated in patients with known hypersensitivity to clarithromycin, to any other macrolide antibiotics, or to any of the excipients.
- Clarithromycin is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of clarithromycin.
- Colchicine is contraindicated in patients with renal or hepatic impairment who are taking P-gp inhibitors or a strong CYP3A4 inhibitor.
- Clarithromycin and ergot derivatives should not be co-administered as this may lead to ergot toxicity.
- Concomitant administration of clarithromycin and any of the following active substances is contraindicated: cisapride, pimozide, astemizole and terfenadine as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsade de pointes.
- Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins), lovastatin or simvastatin, due to the risk of rhabdomyolysis. Treatment with these agents should be discontinued during clarithromycin treatment.
- Clarithromycin should not be administered to patients presenting prolongation of QT-interval.
- Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointes.
- Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

WARNINGS AND PRECAUTIONS:

- 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 dose.
- Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering this antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.
- Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur.
- Due to the risk for QT prolongation, clarithromycin should be used with caution in patients with coronary artery disease, severe cardiac insufficiency, hypomagnesemia, bradycardia or when co-administered with other medicinal products associated with QT prolongation. Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia.
- Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of C. difficile. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Moderate fluid therapy should be performed and adequate treatment initiated. Drugs inhibiting peristaltic should be avoided.
- Exacerbation of symptoms of myasthenia gravis has been reported in patients receiving clarithromycin therapy.
- Clarithromycin therapy for A. pylori may select for drug-resistant organisms.
- 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 initiated.
- Attention should be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs as well as lincomycin and clindamycin.
- There have been post-marketing reports of definitive toxicity with concomitant use of dofetilide/cisapride and clarithromycin, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients. If concomitant administration of clarithromycin and dofetilide/cisapride is unavoidable, patients should be monitored for clinical symptoms of dofetilide toxicity.
- Caution is advised regarding concomitant administration of clarithromycin and tricyclic/tetracyclic compounds, such as triazolam, and midazolam.
- In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS) and Henoch-Schönlein purpura, clarithromycin therapy should be discontinued immediately and appropriate treatment should be started initiated.
- Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme.
- HMG-CoA reductase inhibitors (statins): Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.
- Caution should be exercised when prescribing clarithromycin with statins.
- In instances where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statins. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered.
- Oral hypoglycaemic agents/Insulin: The concomitant use of clarithromycin and oral hypoglycaemic agents and/or insulin can result in significant hypoglycaemia. With certain hypoglycaemic drugs such as repaglinide, nateglinide and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia when used concomitantly. Careful monitoring of glucose is recommended.
- Oral anticoagulants: There is a risk of serious haemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin (See Drug Interactions section). INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

ADVERSE EFFECTS:

The most frequently reported events in adults taking clarithromycin were diarrhoea (5%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%).

Common (Frequency ≥ 1/100 to < 1/10):

Nervous system: Dysgeusia, headache, taste perversion

Psychiatric disorder: Insomnia

Gastrointestinal disorders: Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain

Hepatobiliary system: Abnormal liver function

Skin and subcutaneous tissue disorder: Rash and hyperhidrosis

Uncommon (Frequency ≥ 1/1,000 to < 1/100):

Infections and infestations: Gastroenteritis, candidiasis, vaginal infection

Blood and lymphatic system: Leucopenia, neutropenia, eosinophilia

Metabolism and nutritional disorder: Anorexia, decreased appetite

Psychiatric disorder: Anxiety

Nervous system: Dizziness, tremors, somnolence

Ear and labyrinth disorder: Vertigo, hearing impaired, tinnitus

Cardiac disorder: Palpitations, prolongation of QT interval.

Gastrointestinal disorder: stomatitis, glossitis, anorexia/ anorexia, constipation, dry mouth, eructation, flatulence.

Hepatobiliary system: Cholestasis, hepatitis, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltranferase increased.

Skin and subcutaneous tissue disorder: pruritus, urticaria

General disorders and administration site conditions: Malaise, asthenia, chestpain, chills, fatigue

Investigations: blood alkaline phosphatase increased, blood lactate dehydrogenase increased.

Frequency not known:

Infections and infestations: Pseudomembranous colitis, erysipelas, erythrasma

Blood and lymphatic system: Agranulocytosis, thrombocytopenia

Metabolism and nutritional disorders: Hypoglycemia

Psychiatric disorders: Psychotic disorder, confusional state, depersonalization, depression, disorientation, hallucination, abnormal dreams

Nervous system disorders: Convulsion, ageusia, parosmia, anosmia

Ear and labyrinth disorder: Deafness

Cardiac disorder: Torsade de pointes, ventricular tachycardia

Vascular disorder: hemorrhage

Gastrointestinal disorder: Pancreatitis acute, tongue discoloration, tooth discoloration

Hepatobiliary disorder: Hepatic failure, jaundice hepatocellular

Skin and subcutaneous tissue disorders: Drug rash with eosinophilia and systemic symptoms (DRESS), acne.

Musculoskeletal and connective tissue disorders: Rhabdomyolysis and myopathy

Renal and urinary disorders: Renal failure, nephritis interstitial

Investigations: International normalized ratio increased, prothrombin time prolonged, urine color abnormal

USE IN SPECIAL POPULATION:

Pregnancy: Category C. 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 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.

Paediatric use: Use of clarithromycin tablets are not recommended for children younger than 12 years.

Geriatric use: In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients. Dosage adjustment should be considered in elderly patients with severe renal impairment. Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients.

Renal impairment: Clarithromycin should be used with caution in patients with severe renal impairment. Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearance <30 ml/min (~0.5 ml/s)). If adjustment of dose is necessary, the total daily dosage should be reduced by half. The duration of treatment should not exceed 14 days in these patients.

Hepatic impairment: Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering this antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment. Cases of hepatic dysfunction have been reported with clarithromycin (See Warnings and precautions' section).

DRUG INTERACTIONS:

The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:

Cisapride, pimozide, astemizole and terfenadine: Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly.

Ergotamine/Dihydroergotamine: Co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated.

Effects of other medicinal products on clarithromycin: Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inhibitor administered). Concomitant administration of ritonavir and clarithromycin resulted in an increase in ritonavir, and decrease in clarithromycin serum levels together with an increased rate of events.

The following drugs are known or suspected to affect circulating concentrations of clarithromycin: clarithromycin dosage adjustment or consideration of alternative treatments may be required.

Fluoxetine, nelfinavir, rifampicin, rifabutin and rifapentine: Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14-OH-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Rifampicin: Clarithromycin exposure was decreased by rifampicin; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered, therefore alternatives to clarithromycin should be considered for the treatment of MAC.

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 minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir: A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. 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%. Doses of clarithromycin greater than 1 gm/day should not be co-administered with ritonavir.

Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see section below, Bi-directional drug interactions).

Effect of clarithromycin on other medicinal products

CYP3A based interactions: Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolized by this enzyme.

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.

The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isoenzyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, colchicine, cyclosporin, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole and antocoagulants (e.g. warfarin), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine. Drugs interacting by similar mechanisms through other isoenzymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Antiarrhythmics: There have been post-marketed reports of torsade de pointes occurring with the concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during co-administration of clarithromycin with these drugs. Serum levels of quinidine and disopyramide should be monitored during clarithromycin therapy.

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_{0-24} and $t_{1/2}$ increased by 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 omeprazole was co-administered with clarithromycin.

Sildenafil, tadalafil and vardenafil: Each of these phosphodiesterase inhibitors is metabolized, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these drugs are co-administered with clarithromycin.

Theophylline, carbamazepine: Results of clinical studies indicate that there was a modest but statistically significant (p≤ 0.05) increase of circulating theophylline or carbamazepine levels when either of these drugs were administered concurrently with clarithromycin. Dose reduction may need to be considered.

Tolterodine: The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metabolizer population.

Transcriptional inhibitors (e.g., alprazolam, midazolam, triazolam): When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Other drug interactions

Colchicine: Clarithromycin is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity.

Digoxin: Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concurrently 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.

Zidovudine: Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine to allow for a 4-hour interval between administration. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Proteinase inhibitors: There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolized by CYP3A (e.g., phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.

Bi-directional drug interactions

Ritonavir: Both clarithromycin and ritonavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with ritonavir (400 mg once daily) resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH-clarithromycin, with a 28% increase in the AUC of ritonavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance <30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

Saquinavir: Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, leading to a bi-directional drug interaction. Clarithromycin may increase the plasma levels of saquinavir, while saquinavir may increase the plasma levels of clarithromycin. Patients taking saquinavir and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged cytotoxicity.

Saquinavir: Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in a 45% increase in saquinavir AUC and C_{max} values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are co-administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin.

Ketoconazole: Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

Clarithromycin has been shown not to interact with oral contraceptives.

OVERDOSAGE:

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.

Storage:

Store in a dry place, below 30°C. Protect from light.

Keep away from the reach of children

Presentation: 5 x 10 tablets

Manufactured by

Emcure

PHARMACEUTICALS LTD.

Lane No. 3, Phase-II, IDCO,

Bal-Gronhana, Jammu - 181 133, INDIA.

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Product	Acem - 500	**New / Revised A/W**	Revised A/W	**FDA Lic. Availability**	Avail.
Dosage form	Tablet	**Reason for change**	Change in Storage condition & removal of French text.	**Proof 1**	22.09.2018
Therapeutic Category	Antibiotic	**Colour Scheme**	Black	**Corrections of Proof 1**	Editorial changes
Item	Nigeria Export Pack Insert A/W	**Pantone Shades**	N.A.	**Proof 2**	24.09.2018
Dimension	L. 80 x H. 420 mm (Folded 80 x 52.5 mm)	**Total No. of Colours**	1	**Corrections of Proof 2**	
Substrate	Super white maplitho paper (J. K. Mill)	**Special Effect (if any)**	N.A.	**Proof 3**	
Specification	60 GSM	**Item Code**	514441407NG02	**Corrections of Proof 3**	
Printing Area	B/B	**Marketing Division**	Emcure Export	**Final**	
Item Style	N.A.	**Design / Colour Approved on**	At the time of launching	**A/W Checked by**	PMD Cell
A/W Proportion	Same Size	**Vendor**		**A/W Verified by**	Production / QC
Product Status	Emcure Own Jammu Unit	**Country**	Nigeria	**A/W Approved by**	Unit Head

Remark (If any) : Revised for change in Storage condition & removal of French text.