



CLARITHROMYCIN

CLARIWIN DT 125 mg Dispersible Tablet ANTIBACTERIAL

PRODUCT NAME

Clariwin DT

NAME AND STRENGTH:

Clarithromycin Dispersible Tablets 125mg

PHARMACOLOGIC CATEGORY:

General anti-infectives for systemic use (Anti-bacterial).

PRODUCT DESCRIPTION:

Yellow coloured, flat, circular, bevelledged, uncoated dispersible tablets with a breakline on one surface and plain on other.

FORMULATION/COMPOSITION:

Each dispersible tablet contains:

Clarithromycin 125 mg

[As Clarithromycin Granules (suspension grade) 42%]

PHARMACODYNAMICS/PHARMACOKINETICS:
Pharmacodynamics:

Clarithromycin is an antibiotic belonging to the macrolide antibiotic group. It exerts its antibacterial action by selectively binding to the 50S ribosomal subunit of susceptible bacteria preventing translocation of activated amino acids. It inhibits the intracellular protein synthesis of susceptible bacteria. The 14-hydroxy metabolite of clarithromycin, a product of parent drug metabolism also has antimicrobial activity. The metabolite is less active than the parent compound for most organisms, including mycobacterium spp. An exception is Haemophilus influenza where the 14-hydroxy metabolite is twofold 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*.

Aerobes: 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.*

Pharmacokinetics:

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

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Gram-negative Bacteria: *Haemophilus influenzae*; *Haemophilus para influenzae*; *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*.

Aerobes: Macrolide-susceptible *Bacteroides fragilis*; *Clostridium perfringens*; *Peptococcus species*; *Peptostreptococcus species*; *Propionibacterium acnes*.

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The activity of clarithromycin against *H. pylori* is greater at neutral pH than at acid pH.

INDICATIONS:

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Clarithromycin 250mg Tablets are indicated in adults and children 12 years and older. Clarithromycin is indicated for treatment of infections caused by susceptible organisms. Indications include:

Lower respiratory tract infections for example acute 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 as listed in the microbiology section.

Clarithromycin is also indicated in skin and soft tissue infections of mild to moderate severity (e.g. folliculitis, cellulitis, erysipelas) 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. See Dosage and Administration section.

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Gram-positive Bacteria: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes* (Group A beta-hemolytic streptococci); *alpha haemolytic 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*.

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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.*

The activity of clarithromycin against *H. pylori* is greater at neutral pH than at acid pH.

DOSAGE AND MODE/ROUTE OF ADMINISTRATION:

Clarithromycin will be on the water temperature dispersion or directly after taking oral. Adult usual dose each 0.25g, once every 12 hours; Serious infections each 0.5g, once every 12 hours, or compliance. Children on a daily 10 ~ 15mg per kilogram, two to three hours taking.

Patients with respiratory tract/skin and soft tissue infections

Adults: The usual dose is 250 mg twice daily although this may be increased to 500mg twice daily in severe infections. The usual duration of treatment is 6 to 14 days.

Children older than 12 years: As for adults.

Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability.

Eradication of *H. pylori* in patients with duodenal ulcers (Adults) The usual duration of treatment is 6 to 14 days.

Triple Therapy: Clarithromycin (500mg) twice daily and lansoprazole 30mg twice daily should be given with amoxicillin 1000mg twice daily.

Triple Therapy: Clarithromycin (500mg) twice daily and lansoprazole 30mg twice daily should be given with metronidazole 400mg twice daily.

Triple Therapy: Clarithromycin (500mg) twice daily and omeprazole 40mg daily should be given with amoxicillin 1000mg twice daily.

Triple Therapy: Clarithromycin (500mg) twice daily and omeprazole 20mg daily should be given with amoxicillin 1000mg twice daily.

Elderly: As for adults.

Renal impairment: In patients with renal impairment with creatinine clearance less than 30 mL/min, the dosage of clarithromycin should be reduced by one-half, i.e. 250 mg once daily, or 250 mg twice daily in more severe infections. Treatment should not be continued beyond 14 days in these patients.

CONTRAINDICATIONS & PRECAUTION(S), WARNING(S):

Hypersensitivity to macrolide antibiotic drugs or to any of the excipient

Concomitant administration of clarithromycin and ergot alkaloids (e.g., ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity.

Concomitant administration of clarithromycin and oral midazolam is contraindicated.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, pimozide and terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.

Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes.

Concomitant administration with ticagrelor or ranolazine is contraindicated.

Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4, (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.

As with other strong CYP3A4 inhibitors, Clarithromycin should not be used in patients taking colchicine.

Clarithromycin should not be given to patients with hypokalaemia (risk of prolongation of QT-time).

Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

PRECAUTION & WARNING:

Use of any antimicrobial therapy, such as clarithromycin, to treat *H. pylori* infection may select for drug-resistant organisms. The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy.

Clarithromycin is principally metabolised 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 fatal hepatic failure have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

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.

Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients. Concomitant administration of clarithromycin and colchicine is contraindicated. Caution is advised regarding concomitant administration of clarithromycin and triazole benzodiazepines, such as triazolam, and intravenous or oromucosal midazolam.

Prolongation of the QT Interval: Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides including clarithromycin.

Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsades de pointes), clarithromycin should be used with caution in the following patients:

- Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia
- Patients with electrolyte disturbances such as hypomagnesaemia. Clarithromycin must not be given to patients with hypokalaemia
- Patients concomitantly taking other medicinal products associated with QT prolongation
- Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfenadine is contraindicated
- Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia

Pneumonia: In view of the emerging resistance of *Streptococcus pneumoniae* to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia. In hospital acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

Skin and soft tissue infections of mild to moderate severity: These infections are most often caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed. In cases where beta-lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the drug of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections, such as those caused by *Corynebacterium diphtheriae*, *acne vulgaris*, and *erysipelas* and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g. acute generalised exanthematous pustulosis (AGEP), Stevens - Johnson syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms (DRESS)), clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently 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.

Caution should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathy. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. 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 (such as sulphonylurea) and/or insulin can result in significant hypoglycaemia. 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. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

Long-term use may, as with other antibiotics, result in colonisation with increased numbers of non-susceptible bacteria and fungi. If super infections occur, appropriate therapy should be instituted. Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as Lincomycin and clindamycin.

PREGNANCY AND LACTATION:

Pregnancy: The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryofoetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

Lactation: The safety of clarithromycin for using during breast-feeding of infants has not been established. Clarithromycin is excreted into human breast milk.

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.

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias, such as QT prolongation, ventricular tachycardia, and ventricular fibrillation and torsades de pointes. In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in 2- to 3-fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

extensively metabolised by this enzyme.

Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolised by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

The following drugs or drug classes are known or suspected to be metabolised by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporin, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafl, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine but this list is not exhaustive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Antiarrhythmics

There have been post-marketed reports of torsades de pointes occurring with the concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QT prolongation during coadministration of clarithromycin with these drugs. Serum levels of quinidine and disopyramide should be monitored during clarithromycin therapy.

There have been post marketing reports of Hypoglycemia with the concomitant administration of clarithromycin and disopyramide. Therefore blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

Oral hypoglycaemic agents/Insulin

With certain hypoglycaemic drugs such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause Hypoglycemia when used concomitantly. Careful monitoring of glucose is recommended.

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 (Cmax, AUC0-24, and t1/2 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 metabolised, 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 ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels when either of these drugs were administered concomitantly 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 metaboliser population.

Triazolobenzodiazepines (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. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. Drug delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the drug, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. The same precautions should also apply to other benzodiazepines that are metabolised by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, and 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

Colchicine is a substrate for both CYP3A and the efflux transporter, Pglycoprotein (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.

Digoxin

Digoxin is thought to be a substrate for the efflux transporter, Pglycoprotein (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 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.

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 each medication. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxynosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and Valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolised 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

Atazanavir

Both clarithromycin and atazanavir 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 atazanavir (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 atazanavir. 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 coadministered with protease inhibitors.

Calcium Channel Blockers

Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g. verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradycardia and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

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 steady-state AUC and Cmax values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and Cmax 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 gelatine capsule formulation may not be representative of the effects seen using the saquinavir hard gelatine 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.

Patients taking oral contraceptives should be warned that if diarrhoea, vomiting or breakthrough bleeding occur there is a possibility of contraceptive failure.

ADVERSE DRUG REACTIONS:

a. Summary of the safety profile

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and paediatric populations are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics.

There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without pre-existing mycobacterial infections.

b. Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin immediate-release tablets, granules for oral suspension, powder for solution for injection, extended-release tablets and modified-release tablets.

The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), very rare ($< 1/10,000$) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

System Organ Class		Common	Uncommon	Very rare	Not Known
Infections and infestations		Oral moniliasis	Candidiasis, vaginal infection		Pseudomembranous colitis, erysipelas
Blood and lymphatic system			Leukopenia, neutropenia ¹ , eosinophilia ¹		Agranulocytosis, thrombocytopenia
Immune system disorders			Hypersensitivity		Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite		
Psychiatric disorders		Insomnia	Anxiety	Nightmares	Psychotic disorder, confusional state, depersonalization, depression, disorientation, hallucination, abnormal dreams

Nervous system disorders		Dysgeusia, headache, taste perversion,	Dizziness, somnolence ² , tremor		Convulsion, aguesia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus		Deafness
Cardiac disorders			Electrocardiogram QT prolonged, palpitations		Torsade de pointes, ventricular tachycardia, ventricular fibrillation
Vascular disorders					Haemorrhage
Gastrointestinal disorders		Diarrhoea ³ , vomiting, dyspepsia, nausea, abdominal pain	Gastritis, stomatitis, glossitis, abdominal distension ¹ , constipation, dry mouth, eructation, flatulence		Pancreatitis acute, tongue discoloration, tooth discoloration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis ¹ , hepatitis ¹ , alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased ¹		Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Pruritus, urticaria		Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne
Musculoskeletal and connective tissue disorders					Rhabdomyolysis ⁴ , myopathy
Renal and urinary disorders					Renal failure, nephritis interstitial
General disorders and administration site conditions			Malaise ¹ , asthenia, chest pain ¹ , chills ¹ , fatigue ¹		
Investigations		Elevated BUN (blood urea nitrogen)	Serum creatinine raised, blood alkaline phosphatase increased ¹ , blood lactate dehydrogenase increased ¹		International normalized ratio increased, prothrombin time prolonged urine colour abnormal

¹ADRs reported only for the Immediate-Release Tablets formulation

²See section a)

³See section c)

c. Description of selected adverse reactions

In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol

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.

Special population: Adverse Reactions in Immunocompromised Patients

Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age.

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

e. Other special populations

Immunocompromised patients

In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of Human Immunodeficiency Virus (HIV) disease or intercurrent illness.

In adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 1000 mg and 2000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvate Transaminase (SGPT) elevations. Additional low-frequency events included Dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1000 mg and 2000 mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000 mg of clarithromycin.

In these immunocompromised patients, evaluations of laboratory values were made by analyzing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2% to 3% of those patients who received 1000 mg or 2000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormal values were noted for patients who received 4000 mg daily for all parameters except White Blood Cell.

OVERDOSE AND TREATMENT:

Symptoms

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxemia.

Management

Adverse reactions accompanying over dosage should be treated by the prompt elimination of unabsorbed drug by gastric lavage and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

STORAGE CONDITION:

Store at temperatures below 30°C.

DOSAGE FORMS AND PACKAGING AVAILABLE:

Alu/Alu Strip foil of 10's (Box of 30's)

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):

Not Applicable

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:

Marketing Authorization Holder

Brown & Burk Philippines Inc
U-501, 5/F, SEDCCO 1 Bldg., 120 Rada cor., Legaspi Sts., Legaspi Village, Makati City, Philippines

NAME AND ADDRESS OF MANUFACTURER:

MICRO LABS LIMITED

92, Sipcot Industrial Complex,
Hosur – 635 126, India.

CAUTION STATEMENT:

FOODS, DRUGS, DEVICES, AND COSMETICS ACT PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

ADR REPORTING STATE