SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name:

Clariwin 500

1.2 Strength:

500mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film coated tablet contains Clarithromycin USP…… 500 mg

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clarithromycin tablets are indicated for the treatment of adults with mild to moderate infection caused by susceptible strains of the designated microorganisms in the conditions listed below:

Acute maxillary sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*

Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*

Community-Acquired Pneumonia due to *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Chlamydia pneumoniae* (TWAR), or *Mycoplasma pneumoniae*

4.2 Posology and method of administration

Clarithromycin tablets should be taken with food. Clarithromycin tablets should be swallowed whole and not chewed, broken or crushed.

Clarithromycin may be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function. In patients with severe renal impairment (CLCR < 30 mL/min), the dose of clarithromycin should be reduced by 50%. However, when patients with moderate or severe renal impairment are taking clarithromycin concomitantly with atazanavir or ritonavir, the dose of clarithromycin should be reduced by 50% or 75% for patients with CL_{CR} of 30 to 60 mL/min or < 30 mL/min, respectively.

ADULT DOSAGE GUIDELINES				
	BIAXIN Tablets		BIAXIN XL Tablets	
Infection	Dosage (q12h)	Duration (days)	Dosage (q24h)	Duration (days)
Pharyngitis/Tonsillitis due to				
S. pyogenes	250 mg	10	-	-
Acute maxillary sinusitis due to	500 mg	14	2 x 500 mg	14
H. influenzae				
M. catarrhalis				
S. pneumoniae				
Acute exacerbation of chronic bronchitis due to				
H. influenzae	500 mg	7-14	2 x 500 mg	7
H. parainfluenzae	500 mg	7	2 x 500 mg	7
M. catarrhalis	250 mg	7-14	2 x 500 mg	7
S. pneumoniae	250 mg	7-14	2 x 500 mg	7
Community-Acquired Pneumonia due to				

H. influenzae	250 mg	7	2 x 500 mg	7
H. parainfluenzae	-	-	2 x 500 mg	7
M. catarrhalis	-	-	2 x 500 mg	7
S. pneumoniae	250 mg	7-14	2 x 500 mg	7
C. pneumoniae	250 mg	7-14	2 x 500 mg	7
M. pneumoniae	250 mg	7-14	2 x 500 mg	7
Uncomplicated skin and skin structure	250 mg	7-14	-	-
S. aureus				
S. pyogenes				

4.3 Contraindications

Clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, or any of the macrolide antibiotics.

Clarithromycin is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of clarithromycin.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are coadministered with cisapride, pimozide, astemizole, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

Concomitant administration of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment.

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 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.

4.4 Special warnings and precautions for use

Precautions

General

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.

Exacerbation of symptoms of myasthenia gravis and new onset of symptoms of myasthenic syndrome has been reported in patients receiving clarithromycin therapy.

Information to Patients

Patients should be counselled that antibacterial drugs including Clarithromycin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Clarithromycin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that

bacteria will develop resistance and will not be treatable by Clarithromycin or other antibacterial drugs in the future.

Diarrhoea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Warnings

Use in Pregnancy

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.

Hepatotoxicity

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.

QT Prolongation

Clarithromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of *torsades de pointes* have been spontaneously reported during post marketing surveillance in patients receiving clarithromycin. Fatalities have been reported. Clarithromycin should be avoided in patients with ongoing proarrhythmic conditions such as

uncorrected hypokalemia or hypomagnesaemia, clinically significant bradycardia **and** in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

4.5 Interaction with other medicinal products and other forms of interaction

Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range. 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 Cmax, Cmin, and the area under the serum concentration time curve (AUC) of theophylline increased about 20%.

Hypotension, bradyarrhythmia, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class.

Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered.

When clarithromycin and terfenadine were coadministered, plasma concentrations of the active acid metabolite of terfenadine were threefold higher, on average, than the values observed when terfenadine was administered alone. The pharmacokinetics of clarithromycin and the 14-OH-clarithromycin were not significantly affected by coadministration of terfenadine once clarithromycin reached steady-state conditions. Concomitant administration of clarithromycin with terfenadine is contraindicated.

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 t½ 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.
Coadministration of clarithromycin with ranitidine bismuth citrate resulted in increased plasma ranitidine concentrations (57%), increased plasma bismuth trough concentrations (48%), and increased 14-hydroxyclarithromycin plasma concentrations (31%). These effects are clinically insignificant.

Simultaneous oral administration of Clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Following administration of clarithromycin 500 mg tablets twice daily with zidovudine 100 mg every 4 hours, the steady-state zidovudine AUC decreased 12% compared to administration of zidovudine alone (n=4). Individual values ranged from a decrease of 34% to an increase of 14%. When clarithromycin tablets were administered two to four hours prior to zidovudine, the steady-state zidovudine Cmax increased 100% whereas the AUC was unaffected (n=24). Administration of clarithromycin and zidovudine should be separated by at least two hours. The impact of co-administration of Clarithromycin tablets and zidovudine has not been evaluated.
Simultaneous administration of Clarithromycin tablets and didanosine to 12 HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.
Following administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers, the steady-state clarithromycin Cmin and AUC increased 33% and 18%, respectively. Steady-state concentrations of 14-OH clarithromycin were not significantly affected by concomitant administration of fluconazole. No dosage adjustment of clarithromycin is necessary when co-administered with fluconazole.

Ritonavir

Concomitant administration of clarithromycin and ritonavir (n = 22) 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. Since concentrations of 14-OH clarithromycin are significantly reduced when clarithromycin is co-administered with ritonavir, alternative antibacterial therapy should be

considered for indications other than infections due to *Mycobacterium avium* complex. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

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 is a substrate for P-glycoprotein (Pgp) and clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are co-administered, inhibition of Pgp by clarithromycin may lead to increased exposure of digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have been reported in post-marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Monitoring of serum digoxin concentrations should be considered, especially for patients with digoxin concentrations in the upper therapeutic range.

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 are examples of some clinically significant CYP3A based drug interactions. Interactions with other drugs metabolized by the CYP3A isoform are also possible.

Carbamazepine and Terfenadine

Increased serum concentrations of carbamazepine and the active acid metabolite of terfenadine were observed in clinical trials with clarithromycin.

Colchicine

Colchicine 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 a single dose of colchicine 0.6 mg was administered with clarithromycin 250 mg BID for 7 days, the colchicine Cmax increased 197% and the AUC0-∞ increased 239% compared to administration of colchicine alone. The dose of colchicine should be reduced when co-administered with clarithromycin in patients with normal renal and hepatic function. Concomitant use of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment.

Efavirenz, Nevirapine, Rifampicin, Rifabutin, and Rifapentine

Inducers of CYP3A enzymes, such as efavirenz, Nevirapine, rifampicin, rifabutin, and Rifapentine will increase the metabolism of clarithromycin, thus decreasing plasma concentrations of clarithromycin, while increasing those of 14-OH-clarithromycin. Since the microbiological activities of clarithromycin and 14-OHclarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers. Alternative antibacterial treatment should be considered when treating patients receiving inducers of CYP3A.

Sildenafil, Tadalafil, and Vardenafil

Each of these phosphodiesterase inhibitors is primarily metabolized by CYP3A, and CYP3A will be inhibited by concomitant administration of clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil, or vardenafil will result in increased exposure of these phosphodiesterase inhibitors. Coadministration of these phosphodiesterase inhibitors with clarithromycin is not recommended.

Tolterodine

The primary route of metabolism for tolterodine is via 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. Tolterodine 1 mg twice daily is recommended in patients deficient in CYP2D6 activity (poor metabolizers) when co-administered with clarithromycin.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam)

When a single dose of midazolam was co-administered with clarithromycin tablets (500 mg twice daily for 7 days), midazolam AUC increased 174% after intravenous administration of midazolam and 600% after oral administration. When oral midazolam is co-administered with clarithromycin, dose adjustments may be necessary and possible prolongation and intensity of effect should be anticipated. Caution and appropriate dose adjustments should be considered when triazolam or alprazolam is co-administered with clarithromycin. For benzodiazepines which are not metabolized by CYP3A (e.g., 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.

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bidirectional drug interaction. Following administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily), the clarithromycin AUC increased 94%, the 14-OH clarithromycin AUC decreased 70% and the atazanavir AUC increased 28%. When clarithromycin is co-administered with atazanavir, the dose of clarithromycin should be decreased by 50%. Since concentrations of 14-OH clarithromycin are significantly reduced when clarithromycin is co-administered with atazanavir, alternative antibacterial therapy should be considered for indications other than infections due to *Mycobacterium avium* complex.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, potentially leading to a bidirectional drug interaction when administered concomitantly. Clarithromycin may increase the plasma concentrations of itraconazole, while itraconazole may increase the

plasma concentrations of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged adverse reactions.

Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A and there is evidence of a bidirectional drug interaction. Following administration of clarithromycin (500 mg bid) and saquinavir (soft gelatine capsules, 1200 mg tid) to 12 healthy volunteers, the steady-state saquinavir AUC and Cmax increased 177% and 187% respectively compared to administration of saquinavir alone. Clarithromycin AUC and C max increased 45% and 39% respectively, whereas the 14–OH clarithromycin AUC and Cmax decreased 24% and 34% respectively, compared to administration with clarithromycin alone. No dose adjustment of clarithromycin is necessary when clarithromycin is co-administered with saquinavir in patients with normal renal function. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (refer to interaction between clarithromycin and ritonavir).

The following CYP3A based drug interactions have been observed with erythromycin products and/or with clarithromycin in post-marketing experience:

Antiarrhythmics

There have been post-marketing 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

Post-marketing reports indicate that coadministration 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 with ergotamine or dihydroergotamine is contraindicated.

Triazolobenziodidiazepines (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., atorvastatin, 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 should be considered. (See Viagra package inserts.)

There have been spontaneous or published reports of CYP3A based interactions of erythromycin and/or clarithromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol, Bromocriptine and vinblastine.

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.

4.6 Pregnancy and lactation

Pregnancy

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

Lactation

It is 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. It is known that clarithromycin is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk. Preweaned rats, exposed indirectly via consumption of milk from dams treated with 150 mg/kg/day for 3 weeks, were not adversely affected, despite data indicating higher drug levels in milk than in plasma.

4.7 Effects on ability to drive and use machines

There are no data on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

4.8 Undesirable effects

The majority of side effects observed in clinical trials were of a mild and transient nature. Fewer than 3% of adult patients without mycobacterial infections and fewer than 2% of pediatric patients without mycobacterial infections discontinued therapy because of drug-related side effects. Fewer than 2% of adult patients taking Clarithromycin tablets discontinued therapy because of drug-related side effects.

The most frequently reported events in adults taking Clarithromycin tablets (clarithromycin tablets, USP) were diarrhea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). In pediatric patients, the most frequently reported events were diarrhea (6%), vomiting (6%), abdominal pain (3%), rash (3%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% was described as severe.

The most frequently reported events in adults taking Clarithromycin (Clarithromycin tablets) were diarrhea (6%), abnormal taste (7%), and nausea (3%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, less than 1% was described as severe.

In the acute exacerbation of chronic bronchitis and acute maxillary sinusitis studies overall gastrointestinal adverse events were reported by a similar proportion of patients taking either Clarithromycin tablets; however, patients taking Clarithromycin tablets reported significantly less severe gastrointestinal symptoms compared to patients taking Clarithromycin tablets. In addition, patients taking Clarithromycin tablets had significantly fewer premature discontinuations for drug-related gastrointestinal or abnormal taste adverse events compared to Clarithromycin tablets.

In community-acquired pneumonia studies conducted in adults comparing clarithromycin to erythromycin base or erythromycin stearate, there were fewer adverse events involving the digestive system in clarithromycin-treated patients compared to erythromycin-treated patients (13% vs 32%; $p < 0.01$). Twenty percent of erythromycin-treated patients discontinued therapy due to adverse events compared to 4% of clarithromycin-treated patients.

Post-Marketing Experience

Allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred. Other spontaneously reported adverse events include glossitis, stomatitis, oral moniliasis, anorexia, vomiting, pancreatitis, tongue discoloration, thrombocytopenia, leukopenia, neutropenia, and dizziness. There have been reports of tooth discoloration in patients treated with Clarithromycin. Tooth discoloration is usually reversible with professional dental cleaning. There have been isolated reports of hearing loss, which is usually reversible, occurring chiefly in elderly women. Reports of alterations of the sense of smell including smell loss, usually in conjunction with taste perversion or taste loss have also been reported.

Transient CNS events including anxiety, behavioural changes, confusional states, convulsions, depersonalization, disorientation, hallucinations, insomnia, depression, manic behaviour, nightmares, psychosis, tinnitus, tremor, and vertigo have been reported during post-marketing surveillance. Events usually resolve with discontinuation of the drug.

Adverse reactions related to hepatic dysfunction have been reported in post marketing experience with clarithromycin.

There have been rare reports of hypoglycemia, some of which have occurred in patients taking oral hypoglycemic agents or insulin.

There have been post-marketing reports of Clarithromycin tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times.

As with other macrolides, clarithromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes.

There have been reports of interstitial nephritis coincident with clarithromycin use.

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.

Changes in Laboratory Values

Changes in laboratory values with possible clinical significance were as follows:

Hepatic

Elevated SGPT (ALT) < 1%; SGOT (AST) < 1%; GGT < 1%; alkaline phosphatase < 1%; LDH < 1%; total bilirubin < 1%

Hematologic

Decreased WBC < 1%; elevated prothrombin time 1%

Renal

Elevated BUN 4%; elevated serum creatinine < 1% GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.

4.9 Overdose

Over dosage of clarithromycin can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea.

Adverse reactions accompanying over dosage 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 most *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 has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections:

Gram-positive Microorganisms

Staphylococcus aureus

Streptococcus pneumoniae

Streptococcus pyogenes

Gram-negative Microorganisms

Haemophilus influenzae

Haemophilus parainfluenzae

Moraxella catarrhalis

Other Microorganisms

Mycoplasma pneumoniae

Chlamydia pneumoniae (TWAR)

Mycobacteria

Mycobacterium avium complex (MAC) consisting of:

Mycobacterium avium

Mycobacterium intracellulare

Beta-lactamase production should have no effect on clarithromycin activity.

5.2 Pharmacokinetic properties

Absorption

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 2.5 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 antimicrobials active metabolite, 14-OH clarithromycin or its peak plasma concentration but does slightly decrease the extent of metabolite 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.

Distribution and Metabolism

In nonfasting 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 8 to 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 5 to 6 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.

Elimination

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%. In comparison, after an oral dose of 250 mg (125 mg/5 mL) suspension every 12 hours, approximately 40% is excreted in urine as clarithromycin. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. 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.

5.3 Preclinical safety data

In acute mouse and rat studies, the median lethal dose was greater than the highest feasible dose for administration (5g/kg).

In repeated dose studies, toxicity was related to dose, duration of treatment and species. Dogs were more sensitive than primates or rats. The major clinical signs at toxic doses included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. In all species the liver was the primary target organ at toxic doses. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected included the stomach, thymus and other lymphoid tissues and the kidneys. At near therapeutic doses, conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.

Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Spraque-Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomolgous monkeys failed to demonstrate any teratogenicity from Clarithromycin. However, a further similar study in Sprague-Dawley rats indicated a low (6%) incidence of cardiovascular abnormalities, which appeared to be due to spontaneous expression of genetic changes. Two

mouse studies revealed a variable incidence (3-30%) of cleft palate and embryonic loss was seen in monkeys but only at dose levels, which were clearly toxic to the mothers.

6. Pharmaceutical Particulars

6.1 List of excipients

Clarithromycin-500mg

MICROCRYSTALLINE CELLULOSE USP
STARCH USP (MAIZE - DRIED)
SORBIC ACID USP
SORBITAN MONOOLEATE USP
POVIDONE USP (K-30)
COLLOIDAL SILICON DIOXIDE USP
MAGNESIUM STEARATE USP
TALC USP
CROSCARMELLOSE SODIUM USP
STEARIC ACID USP
HYPROMELLOSE USP (HPMC 15CPS)
TITANIUM DIOXIDE USP
PROPYLENE GLYCOL USP
LAKE OF QUINOLINE YELLOW
ISOPROPLY ALCOHOL USP
METHYLENE CHLORIDE USP
VANILLA DRY FLAVOUR (VITAL)

6.2 Incompatibilities

None known

6.3 Shelf life

36 Months from the date of manufacture.

6.4 Special precautions for storage

Store below 30°C. Keep out from the reach of children.

6.5 Nature and contents of container

Alu/Alu Blister Pack of 10 Tablets, such 1 blister is packed in a carton along with pack insert

6.6 Special precautions for disposal and other handling

Not applicable

7. Marketing Authorization Holder:

MICRO LABS LIMITED

Micro Labs Limited,
No. 27, Race Course Road, Bangalore 560 001, Karnataka, India
Phones: +91 80 2237 0451-57
Fax : +91 80 2237 0463
Website: www.microlabsltd.com
Email Address: info@microlabs.in

8. Marketing Authorization Numbers

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9. Date of first authorization

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10. Date of revision of the text

April 2018