SUMMARY OFPRODUCTCHARACTERISTICS

MEDOPHARM,INDIA

1. NAME OF THE FINISHED PHARMACEUTICALPRODUCT

Clarithromycin tablets USP500mg(MEDICLAR-500)

2. QUALITATIVE AND QUANTITATIVECOMPOSITION:

Each film coated tablet contains:

Clarithromycin USP 500mg

Refer Excipients section 6.1

3. PHARMACEUTICALFORM

White, oval shaped film coated tablet.

4. Clinicalparticulars

4.1 Therapeuticindications

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

Clarithromycin is indicated in adults and children 12 years and older.

Clarithromycin is indicated for the treatment of thefollowing infections caused byclarithromycin susceptible organisms.

- Bacterial pharyngitis
- Mild to moderate community-acquired pneumonia
- Acute bacterial sinusitis (adequately diagnosed)
- Acute exacerbation of chronic bronchitis
- Skin and soft tissue infections of mild to moderate severity.
- In appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer
- healing medicinal product for the eradication of *Helicobacter pylori* in adult patients with*Helicobacter pylori*-associated ulcers.

4.2 Posology and method of administration

Posology:

The dosage of Clarithromycin film-coated tablets depends on the type and severity of theinfection and has to be defined in any case by the physician.

Adults:

- Standard dosage: The usual dose is 250mg twice daily (in the morning and in the evening)

- High dosage treatment (severe infections): The usual dose may be increased to 500 mgtwice daily in severe infections.

Children older than 12 years: As for adults.

Children younger than 12 years: Use of Clarithromycin 250mg Tablets are notrecommended for children younger than 12 years. Use clarithromycin PaediatricSuspension.

Eradication of Helicobacter pylori in adults:

In patients with gastro-duodenal ulcers due to *Helicobacter pylori* infection clarithromycin isgiven in a dosage of 500 mg twice daily. The national recommendations for *Helicobacterpylori* eradication have to be considered.

Duration of therapy:

The duration of therapy with clarithromycin depends on the type and severity of the infection.The usual duration of treatment is 7 to 14 days.

Dosage in renal functional 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 totaldaily dosage should be reduced by half.

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

Patients with hepatic impairment:

Caution should be exercised when administrating clarithromycin in patients with hepaticimpairment.

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.

4.3 Contraindications

- Clarithromycin is contra-indicated in patients with known hypersensitivity to clarithromycin, to any other macrolide antibiotics, or to any of the excipients listed in section 6.1.
- Concomitant administration of clarithromycin and ergot alkaloids (e.g. ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity (see section 4.5).
- Concomitant administration of clarithromycin and oral midazolam is contraindicated (see section 4.5).
- 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 torsade de pointes (see Section 4.5).

- Clarithromycin should not be given to patients with a history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsade de pointes (see sections 4.4 and 4.5).
- 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 (see section 4.5).
- As with other strong CYP3A4 inhibitors, Clarithromycin should not be used in patients taking colchicine (see sections 4.4 and 4.5).
- Clarithromycin should not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of the QT interval).
- Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
- Concomitant administration of clarithromycin and lomitapide is contraindicated (see
- section 4.5).

4.4 Special warnings and precautions for use

Clarithromycin therapy for *H. pylori* may select for drug-resistant organisms..

The physician should not prescribe clarithromycin to pregnant women without carefullyweighing the benefits against risk; particularly during the first three months of pregnancy(see section 4.6).

Caution is advised in patients with severe renal insufficiency (see section 4.2).

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 fatal hepatic failure (see section 4.8) have been reported. Some patients may havehad pre-existing hepatic disease or may have been taking other hepatotoxic medicinalproducts. Patients should be advised to stop treatment and contact their doctor if signs andsymptoms of

hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, ortender abdomen.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, includingmacrolides, and may range in severity from mild to life-threatening. *Clostridium difficile*associateddiarrhoea (CDAD) has been reported with use of nearly all antibacterial agentsincluding 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 toovergrowth of *C. difficile*. CDAD must be considered in all patients who present withdiarrhoea following antibiotic use. Careful medical history is necessary since CDAD hasbeen reported to occur over two months after the administration of antibacterial agents.

Therefore, discontinuation of clarithromycin therapy should be considered regardless ofthe 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 ofclarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see section 4.5).

Concomitant administration of clarithromycin and colchicine is contraindicated (seesection 4.3).

Caution is advised regarding concomitant administration of clarithromycin andtriazolobenzodiazepines, such as triazolam, and intravenous or oromucosal midazolam(see section 4.5).

Cardiovascular Events

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiacarrhythmia and *torsades de pointes*, have been seen in treatment with macrolides including

clarithromycin (see section 4.8). Therefore as the following situations may lead to anincreased risk for ventricular arrhythmias (including *torsades de pointes),* clarithromycinshould be used with caution in the following patients;

- Patients with coronary artery disease, severe cardiac insufficiency, conductiondisturbances or clinically relevant bradycardia
- Clarithromycin must not be given to patients with hypokalaemia (see section 4.3).
- Patients concomitantly taking other medicinal products associated with QTprolongation (see section 4.5).
- Concomitant administration of clarithromycin with astemizole, cisapride, pimozideand

terfenadine is contraindicated (see section 4.3). Clarithromycin must not be usedin patients with congenital or documented acquired QT prolongation or history ofventricular arrhythmia (see section 4.3).

Epidemiological studies investigating the risk of adverse cardiovascular outcomes withmacrolides have shown variable results. Some observational studies have identified a rareshort-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associatedwith macrolides including clarithromycin. Consideration of these findings should be balancedwith treatment benefits when prescribing clarithromycin.

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

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

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g. Acute generalised exanthematouspustulosis (AGEP),Stevens-Johnson Syndrome, toxic epidermal necrolysis, and DRESS, clarithromycin therapyshould 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 (see section 4.5).

HMG-CoA Reductase Inhibitors (statins): Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3). Caution should be exercised whenprescribing 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

notdependent on CYP3A metabolism (e.g. fluvastatin) can be considered (see section 4.5).

Oral hypoglycaemic agents/Insulin: The concomitant use of clarithromycin and oralhypoglycaemic agents (such as sulphonylurias) and/or insulin can result in significanthypoglycaemia. Careful monitoring of glucose is recommended (see section 4.5).

Oral anticoagulants: There is a risk of serious haemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is coadministeredwith warfarin (see section 4.5). INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently. Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban and apixaban, particularly to patients at high risk of bleeding (see section 4.5).

Hydroxychloroquine or chloroquine: Carefully consider the balance of benefits and risks before prescribing clarithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5)

Long-term use may, as with other antibiotics, result in colonisation with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should beinstituted.

Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

Contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactosemalabsorption should not take this medicine.

Contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

Cisapride, pimozide, astemizole and terfenadine

Elevated cisapride levels have been reported in patients receiving clarithromycin andcisapride concomitantly. This may result in QT prolongation and cardiac arrhythmiasincluding ventricular

tachycardia, ventricular fibrillation and torsades de pointes. Similareffects have been observed in patients taking clarithromycin and pimozide concomitantly (seesection 4.3).

Macrolides have been reported to alter the metabolism of terfenadine resulting in increasedlevels of terfenadine which has occasionally been associated with cardiac arrhythmias, suchas QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes(see section 4.3).

In one study in 14 healthy volunteers, the concomitant administration of clarithromycin andterfenadine resulted in 2- to 3-fold increase in the serum level of the acid metabolite ofterfenadine and in prolongation of the QT interval which did not lead to any clinicallydetectable effect. Similar effects have been observed with concomitant administration ofastemizole and other macrolides.

Ergot alkaloids

Post-marketing reports indicate that co-administration of clarithromycin with ergotamine ordihydroergotamine 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(see section 4.3).

Oral Midazolam

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily),midazolam AUC was increased 7-fold after oral administration of midazolam. Concomitantadministration of oral midazolam and clarithromycin is contraindicated.

HMG-CoA Reductase Inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see 4.3)as these statins are extensively metabolized by CYP3A4 and concomitant treatment withclarithromycin increases their plasma concentration, which increases the risk of myopathy,including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients takingclarithromycin concomitantly with these statins. If treatment with clarithromycin cannot beavoided, therapy with lovastatin or simvastatin must be suspended during the course oftreatment.

Caution should be exercised when prescribing clarithromycin with statins. In situations wherethe concomitant use of clarithromycin with statins cannot be avoided, it is recommended toprescribe the lowest registered dose of the statin. Use of a statin that is not dependent onCYP3A metabolism (e.g.fluvastatin) can be considered. Patients should be monitored forsigns and symptoms of myopathy.

Lomitapide

Concomitant administration of clarithromycin with lomitapide is contraindicated due to thepotential for markedly increased transaminases (see section 4.3).

Hydroxychloroquine or chloroquine

Observational data have shown that co-administration of azithromycin withhydroxychloroquine in patients with rheumatoid arthritis is associated with an increased riskof cardiovascular events and cardiovascular mortality. Because of the potential for a similarrisk with other macrolides when used in combination with hydroxychloroquine orchloroquine, careful consideration should be given to the balance of benefits and risks beforeprescribing clarithromycin for any patients taking hydroxychloroquine or chloroquine. .

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 subtherapeuticlevels of clarithromycin leading to reduced efficacy. Furthermore, it might be

necessary to monitor the plasma levels of the CYP3A inducer, which could be increasedowing to the inhibition of CYP3A by clarithromycin (see also the relevant productinformation for the CYP3A4 inhibitor administered). Concomitant administration of rifabutinand clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serumlevels together with an increased risk of uveitis.

The following drugs are known or suspected to affect circulating concentrations ofclarithromycin; clarithromycin dosage adjustment or consideration of alternative treatmentsmay be required.

Efavirenz, nevirapine, 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 andthus lower the plasma levels of clarithromycin, while increasing those of 14-OHclarithromycin,a metabolite that is also microbiologically active. Since the microbiologicalactivities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, theintended therapeutic effect could be impaired during concomitant administration ofclarithromycin and enzyme inducers.

Etravirine

Clarithromycin exposure was decreased by etravirine; however, concentrations of the activemetabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin hasreduced activity against Mycobacterium avium complex (MAC), overall activity against thispathogen may be altered; therefore alternatives to clarithromycin should be considered for thetreatment of MAC.

Fluconazole:

Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twicedaily to 21 healthy volunteers led to increases in the mean steady-state minimumclarithromycin concentration (Cmin) and area under the curve (AUC) of 33% and 18%respectively. Steady state concentrations of the active metabolite 14(R)-hydroxyclarithromycinwere 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 200mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a markedinhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%,Cmin increased 182% and AUC increased by 77% with concomitant administration ofritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin wasnoted. Because of the large therapeutic window for clarithromycin, no dosage reductionshould be necessary in patients with normal renal function. However, for patients with renalimpairment, the following dosage adjustments should be considered: For patients withCLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patientswith CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses ofclarithromycin greater than 1 gm/day should not be co-administered with ritonavir.

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

The effect of clarithromycin on other medicinal products

CYP3A-based interactions

Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarilymetabolised by CYP3A may be associated with elevations in drug concentrations that couldincrease or prolong both therapeutic and adverse effects of the concomitant drug.

Clarithromycin should be used with caution in patients receiving treatment with other drugsknown to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrowsafety margin (e.g. carbamazepine) and/or the substrate is extensively metabolised by thisenzyme.

Dosage adjustments may be considered, and when possible, serum concentrations of drugsprimarily metabolised by CYP3A should be monitored closely in patients concurrentlyreceiving clarithromycin.

The following drugs or drug classes are known or suspected to be metabolised by the sameCYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporin,disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oralanticoagulants (e.g. warfarin, rivaroxaban, apixaban, see 4.4), atypical antipsychotics (e.g.quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus,terfenadine, triazolam and

vinblastine but this list is not exhaustive. Drugs interacting bysimilar mechanisms through other isozymes within the cytochrome P450 system includephenytoin, theophylline and valproate.

Antiarrhythmics

There have been post-marketed reports of torsades de pointes occurring with the concurrentuse of clarithromycin and quinidine or disopyramide. Electrocardiograms should bemonitored for QT prolongation during co-administration of clarithromycin with these drugs.

Serum levels of quinidine and disopyramide should be monitored during clarithromycintherapy.

There have been post marketing reports of hypoglycemia with the concomitant administrationof clarithromycin and disopyramide. Therefore blood glucose levels should be monitoredduring concomitant administration of clarithromycin and disopyramide.

Oral hypoglycemic agents/Insulin

With certain hypoglycemic drugs such as nateglinide, and repaglinide, inhibition of CYP3Aenzyme by clarithromycin may be involved and could cause hypolgycemia when usedconcomitantly. Careful monitoring of glucose is recommended.

Omeprazole

Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mgdaily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole wereincreased (Cmax, AUC0-24, and t1/2 increased by 30%, 89%, and 34%, respectively), by theconcomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2when omeprazole was administered alone and 5.7 when omeprazole was co-administered withclarithromycin.

Sildenafil, tadalafil and vardenafil

Each of these phosphodiesterase inhibitors is metabolised, at least in part, by CYP3A, andCYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration ofclarithromycin with sildenafil, tadalafil or vardenafil would likely result in increasedphosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosagesshould 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 drugswere administered concomitantly with clarithromycin. Dose reduction may need to beconsidered.

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 pathwayof metabolism is via CYP3A. In this population subset, inhibition of CYP3A results

insignificantly higher serum concentrations of tolterodine. A reduction in tolterodine dosagemay be necessary in the presence of CYP3A inhibitors, such as clarithromycin in theCYP2D6 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. Ifintravenous midazolam is co-administered with clarithromycin, the patient must be closelymonitored 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 similarinteraction to that observed after intravenous midazolam rather than oral administration. Thesame 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, 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 clarithromycinand triazolam. Monitoring the patient for increased CNS pharmacological effects issuggested.

Direct acting oral anticoagulants (DOACs)

The DOAC dabigatran is a substrate for the efflux transporter P-gp. Rivaroxaban andapixaban are metabolised via CYP3A4 and are also substrates for P-gp. Caution should beexercised when clarithromycin is co-administered with these agents particularly to patients athigh risk of bleeding (see section 4.4).

Other drug interactions

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. Whenclarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A byclarithromycin may lead to increased exposure to colchicine (see section 4.3 and 4.4).

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 administeredtogether, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin.

Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxinconcomitantly have also been reported in post marketing surveillance. Some patients

haveshown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias.

Serum digoxin concentrations should be carefully monitored while patients are receivingdigoxin and clarithromycin simultaneously.

Zidovudine

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infectedadult patients may result in decreased steady-state zidovudine concentrations. Becauseclarithromycin appears to interfere with the absorption of simultaneously administered oralzidovudine, this interaction can be largely avoided by staggering the doses of clarithromycinand zidovudine to allow for a 4-hour interval between each medication. This interaction doesnot appear to occur in paediatric HIV-infected patients taking clarithromycin suspension withzidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin isadministered 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. phenytoinand valproate). Serum level determinations are recommended for these drugs whenadministered concomitantly with clarithromycin. Increased serum levels have been reported.

Bidirectional pharmacokinetic interactions

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there isevidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mgtwice daily) with atazanavir (400 mg once daily) resulted in a 2-fold increase in exposure toclarithromycin and a 70% decrease in exposure to 14(R)-hydroxyclarithromycin, with a 28%increase in the AUC of atazanavir.

Because of the large therapeutic window for clarithromycin, no dosage reduction should benecessary in patients with normal renal function.

For patients with moderate renal function (creatinine clearance 30 to 60 ml/min), the dose ofclarithromycin should be decreased by 50%.

For patients with creatinine clearance <30 ml/min, the dose of clarithromycin should bedecreased by 75% using an appropriate clarithromycin formulation, such as immediatereleasetablets, sachet, or paediatric suspensions (not all presentations may be marketed).

Doses of clarithromycin greater than 1000 mg per day should not be co-administered withprotease inhibitors.

Calcium Channel Blockers

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

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to abidirectional 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 closelyfor signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there isevidence of a bidirectional drug interaction.

Concomitant administration of clarithromycin (500 mg bid) and saquinavir (soft gelatinecapsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state area under the curve(AUC) and maximum concentration (Cmax) values of saquinavir, which were 177% and187% higher than those seen with saquinavir alone.

Clarithromycin AUC and Cmax values were approximately 40% higher than those seen withclarithromycin alone.

No dose adjustment is required when the two drugs are co-administered for a limited time atthe doses/formulations studied.

Observations from drug interaction studies using the soft gelatin capsule formulation may notbe representative of the effects seen using the saquinavir hard gelatin capsule.

Observations from drug interaction studies done with unboostedsaquinavir may not berepresentative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is coadministeredwith ritonavir, consideration should be given to the potential effects ofritonavir on clarithromycin (see section above, effect of other medicinal products onclarithromycin).

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

The safety of clarithromycin for use during pregnancy has not been established. Based

onvariable results obtained from animal studies and experience in humans, the possibility ofadverse effects on embryofoetal development cannot be excluded. Some observational studiesevaluating exposure to clarithromycin during the first and second trimester have reported anincreased risk of miscarriage compared to no antibiotic use or other antibiotic use during thesame period. The available epidemiological studies on the risk of major congenitalmalformations with use of macrolides including clarithromycin during pregnancy provideconflicting results.

Therefore, use during pregnancy is not advised without carefully weighing the benefitsagainst risks.

Breast-feeding

The safety of clarithromycin for using during breast-feeding of infants has not beenestablished. Clarithromycin is excreted into human breast milk in small amounts. It has beenestimated that an exclusively breastfed infant would receive about 1.7% of the maternalweight-adjusted dose of clarithromycin.

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 usemachines. The potential for dizziness, vertigo, confusion and disorientation, whichmay occur with the medication, should be taken into account before patients drive oruse machines.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent and common adverse reactions related to clarithromycin therapyfor both adult and paediatric populations are abdominal pain, diarrhoea, nausea,vomiting and taste perversion. These adverse reactions are usually mild in intensityand are consistent with the known safety profile of macrolide antibiotics (see sectionb of section 4.8).

There was no significant difference in the incidence of these gastrointestinal adversereactions 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 frompost-marketing experience with clarithromycin immediate-release tablets, granulesfor oral suspension, powder for solution for injection, extended-release tablets andmodified-release tablets.

The reactions considered at least possibly related to clarithromycin are displayed bysystem organ class and frequency using the following convention: very common(≥1/10), common (≥1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and notknown (adverse reactions from post-marketing experience; cannot be estimated fromthe available data). Within each frequency grouping, adverse reactions are presentedin order of decreasing seriousness when the seriousness could be assessed.

SystemOrgan Class	Very common≥1/10	Common ≥1/100 to < 1/10	Uncommon ≥1/1,000 to <1/100	NotKnown* (cannotbe estimated fromthe available data)
Infectionsand infestations			Cellulitis[1], candidiasis, gastroenteritis[2], infection[3],vaginal infection	Pseudomembranou scolitis, erysipelas,
Bloodand lymphaticsystem			Leukopenia, neutropenia[4], thrombocythaemia[3], eosinophilia[4]	Agranulocyto sis, thrombocytopenia
Immune disorders			Anaphylactoid reaction[1], hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	

Psychatric disorders		Insomnia	Anxiety, nervousness[3]	Psychotic disorder, confusional state[5], depersonalisat ion, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache, taste perversion	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[5], tremor	Convulsion, ageusia, parosmia, anosmia paraesthesia
Ear and labyrinth disorders			Vertigo,hearing impaired, tinnitus	Deafness
Cardiacdisorders			Cardiacarrest[1], atrial fibrillation[1], electrocardiogram QT prolonged, extrasystoles[1], palpitations	Torsadede pointes, ventricular tachycardia, ventricular fibrillation
Vascular disorders		Vasodilation[1]		Haemorrhage[9]
Respiratory, thoracic and mediastinal disorder			Asthma[1], epistaxis[2], pulmonary embolism[1]	

Gastrointestinal disorders		Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain	Oesphagitis[1], gastrooesophageal refluxdisease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence,	Pancreatitis acute, tongue discolouration , tooth discolouration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased,gamma-glutamyltransferase increased[4]	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous		Rash, hyperhydrosis	Dermatitis bullous[1], pruritus, urticaria,	Severe cutaneous

tissuedisorders			rash maculo-papular[3]	adverse reactions (SCAR) (e.g. Acute generalisedexanthematou s pustulosis (AGEP), Stevens- Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS),
Musculoskeletal and connective tissue disorders			Musclespasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis[2,6], myopathy
Renal and urinary disorders			Blood creatinine increased[1], blood ureaincreased[1]	Renal failure, nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis[1]	Injection site pain[1], injection site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]	
Investigations			Albumin globulin ratio abnormal[1], blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4]	International normalised ratio increased[9], prothrombin time prolonged[9], urine color abnormal

1 ADRs reported only for the Powder for Solution for Injection formulation

2ADRs reported only for the Extended-Release Tablets formulation

3 ADRs reported only for the Granules for Oral Suspension formulation

4 ADRs reported only for the Immediate-Release Tablets formulation

5,6 See section c)

** Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.*

c. Description of selected adverse reactions

Injection site phlebitis, injection site pain, and injection site inflammation are specificto the clarithromycin intravenous formulation.

In some of the reports of rhabdomyolysis, clarithromycin was administeredconcomitantly with statins, fibrates, colchicine or allopurinol (see section 4.3 and4.4).

There have been post-marketing reports of drug interactions and central nervoussystem (CNS) effects (e.g. somnolence and confusion) with the concomitant use ofclarithromycin and triazolam. Monitoring the patient for increased CNSpharmacological effects is suggested (see section 4.5).

There have been rare reports of clarithromycin ER tablets in the stool, many of whichhave occurred in patients with anatomic (including ileostomy or colostomy) orfunctional gastrointestinal disorders with shortened GI transit times. In severalreports, tablet residues have occurred in the context of diarrhoea. It is recommendedthat patients who experience tablet residue in the stool and no improvement in theircondition should be switched to a different clarithromycin formulation (e.g.

suspension) or another antibiotic.

Special population: Adverse Reactions in Immunocompromised Patients (see sectione).

d. Paediatric populations

Clinical trials have been conducted using clarithromycin paediatric suspension inchildren 6 months to 12 years of age. Therefore, children under 12 years of ageshould use clarithromycin paediatric suspension.

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

e. *Other special populations*

Immunocompromised patients

In AIDS and other immunocompromised patients treated with the higher doses ofclarithromycin over

long periods of time for mycobacterial infections, it was oftendifficult to distinguish adverse events possibly associated with clarithromycinadministration from underlying signs of Human Immunodeficiency Virus (HIV)disease or intercurrent illness.

In adult patients, the most frequently reported adverse reactions by patients treatedwith total daily doses of 1000 mg and 2000mg of clarithromycin were: nausea,vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache,constipation, hearing disturbance, Serum Glutamic OxaloaceticTransaminase (SGOT) and Serum Glutamic Pyruvate Transaminase (SGPT)elevations. Additional low-frequency events included dyspnoea, insomnia and drymouth. The incidences were comparable for patients treated with 1000mg and2000mg, but were generally about 3 to 4 times as frequent for those patients whoreceived total daily doses of 4000mg of clarithromycin.In these immunocompromised patients, evaluations of laboratory values were madeby analysing those values outside the seriously abnormal level (i.e. the extreme highor low limit) for the specified test. On the basis of these criteria, about 2% to 3% ofthose patients who received 1000mg or 2000mg of clarithromycin daily had seriouslyabnormal elevated levels of SGOT and SGPT, and abnormally low white blood celland platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormalvalues were noted for patients who received 4000mg daily for all parameters exceptWhite Blood Cell.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinalproduct is important. It allows continued monitoring of the benefit/risk balanceof the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme(www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in theGooglePlay or Apple App Store.

4.9 Overdose

Symptoms of intoxification:

Reports indicate that the ingestion of large amounts of clarithromycin can be expectedto produce gastro-intestinal symptoms. One patient who had a history of bipolardisorder ingested 8 grams of clarithromycin and showed altered mental status,paranoid behaviour, hypokaliaemia and hypoxaemia.

Therapy of intoxification:

Adverse reactions accompanying overdosage should be treated by the promptelimination of unabsorbed drug and supportive measures. As with other macrolides,clarithromycin serum levels are not expected to be appreciably affected byhaemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:*Macrolides*

ATC code:J01FA09.

Mechanism of action:

Clarithromycin is an antibiotic belonging to the macrolide antibiotic group. It exertsits antibacterial action by selectively binding to the 50s ribosomal sub-unit ofsusceptible bacteria preventing translocation of activitate amino acids. It inhibits theintracellular protein synthesis of susceptible bacteria.

The 14-(R)-hydroxy metabolite of clarithromycin also has antimicrobial activity. Themetabolite is less active than the parent compound for most organisms, includingmycobacterium spp. An xception is Haemophilus influenza where the 14-hydroxymetabolite is two-fold more active than the parent compound.

Clarithromycin is usually active against the following organisms in vitro:

Gram-positive Bacteria: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes*(Group A beta-hemolytic streptococci); alphahemolytic streptococci (viridans group); *Streptococcus (Diplococcus) pneumoniae; Streptococcus agalactiae; Listeria monocytogenes.*

Gram-negative Bacteria: *Haemophilus influenza; Haemophilusparainfluenza; Moraxella (Branhamella) catarrhalis; Neisseria gonorrhoeae; Legionella pneumophila; Bordetella pertussis; Campylobacter jejuni.*

Mycoplasma: *Mycoplasma pneumoniae; Ureaplasmaurealyticum.*

Other Organisms: *Chlamydia trachomatis; Mycobacterium avium; Mycobacterium leprae; Mycobacterium kansasii; Mycobacterium chelonae; Mycobacterium fortuitum; Mycobacterium intracellularis; Chlamydia pneumoniae.*

Anaerobes: *Clostridium perfringens*; Peptococcus species; Peptostreptococcus species; *Propionibacterium acnes*.

Clarithromycin has bactericidal activity against several bacterial strains. The organisms include *Haemophilusinfluenzae; Streptococcus pneumoniae; Streptococcus pyogenes; Streptococcus agalactiae; Moraxella (Branhamella) catarrhalis; Neisseria gonorrhoeae*and Campylobacter spp.

Breakpoints

The following breakpoints have been established by the European Committee forAntimicrobial Susceptibility Testing (EUCAST).

Breakpoints (MIC, mg/L)		
Microorganism	**Susceptible (≤)**	**Resistant(>)**
Staphylococcusspp.	1mg/L	2mg/L
Streptococcus A, B, C andG	0.25mg/L	0.5 mg/L
Streptococcuspneumonia	0.25mg/L	0.5 mg/L
Viridans groupstreptococcus	IE	IE
Haemophilusspp.	1mg/L	32mg/L
Moraxellacatarrhalis	0.25mg/L	0.5 mg/L[1]
Helicobacterpylori	0.25mg/L[1]	0.5 mg/L
[1] The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguishwild-type isolates from those with reducessusceptibility. "IE"indicatesthatthereisinsufficientevidencethatthespeciesinquestionisagoodtargetfortherapy with thedrug.		

5.2Pharmacokineticproperties

Absorption

Clarithromycin is rapidly and well absorbed from the gastrointestinal tract –primarily in the jejunum – but undergoes extensive first-pass metabolism afteroral administration. The absolute bioavailability of a 250-mg clarithromycintablet is approximately 50%. Food slightly delays the absorption but does not affect the extent of bioavailability. Therefore, clarithromycin tablets may begiven without regard tofood. Due to its chemical structure (6-OMethylerythromycin)clarithromycin is quite resistant to degradation bystomach acid. Peak plasma levels of 1 – 2 μg/ml clarithromycin were observedin adults after oral administration of 250 mg twice daily. After administrationof 500 mg clarithromycin twice daily the peak plasma level was 2.8 μg/ml.After administration of 250 mg clarithromycin twice daily the microbiologically active 14-hydroxy metabolite attains peak plasmaconcentrations of 0.6 μg/ml. Steady state is attained within 2 days of dosing.

Distribution

Clarithromycin penetrates well into different compartments, with an estimated volume of distribution of 200-400 L. Clarithromycin provides concentrations in some tissues that are several times higher than the circulating level of the active substance. Increased levels have been found in both tonsils and lung tissue. Clarithromycin also penetrates the gastric mucus.

Clarithromycin is approximately 70% bound to plasma proteins at therapeutic levels.

Biotransformation and elimination:

Clarithromycin is rapidly and extensively metabolised in the liver. Metabolism is inthe liver involving the P450 cytochrome system. Three metabolites are described: Ndemethylclarithromycin, decladinosyl clarithromycin and 14-hydroxyclarithromycin.

The pharmacokinetics of clarithromycin is non-linear due to saturation of hepaticmetabolism at high doses. Elimination half-life increased from 2-4 hours followingadministration of 250 mg clarithromycin twice daily to 5 hours followingadministration of 500 mg clarithromycin twice daily. The half-life of the active 14-hydroxy metabolite ranges between 5 to 6 hours following administration of 250 mg clarithromycin twice daily

Approximately 20 -40% of clarithromycin is excreted as the unchanged activesubstance in the urine. This proportion is increased when the dose is increased. Andditional 10% to 15% is excreted in the urine as 14-hydroxy metabolite. The rest isexcreted in the faeces. Renal insufficiency increases clarithromycin levels in plasma,if the dose is not decreased.

Total plasma clearance has been estimated to approximately 700 ml/min (11.7ml/s), with a renal clearance of approximately 170 ml/min (2.8 ml/s).

SPECIAL POPULATIONS:

Renal impairment: Reduced renal insufficiency function results in increased plasmalevels of clarithromycin and the active metabolite levels in plasma.

5.3 Preclinical safety data

In 4-week-studies in animals, toxicity of clarithromycin was found to be related to thedose and to the duration of the treatment. In all species, the first signs of toxicity wereobserved in the liver, in which lesions were seen within 14 days in dogs andmonkeys. The levels of systemic exposure at which this toxicity occurred are notknown in detail, but toxic doses (300 mg/kg/day) were clearly higher than the therapeutic doses recommended for humans. Other tissues affected included thestomach, thymus and other lymphoid tissues as well as the kidneys. At neartherapeutic doses conjunctival injection and lacrimation occurred only in dogs. At adose of 400mg/kg/day some dogs and monkeys developed corneal opacities and/oroedema.

In vitro and *in vivo* studies showed that clarithromycin did not have genotoxicpotential.

Studies on reproduction toxicity showed that administration of clarithromycin atdoses 2x the clinical

dose in rabbit (iv) and 10x the clinical dose in monkey (po)resulted in an increased incidence of spontaneous abortions. These doses were relatedto maternal toxicity. No embryotoxicity or teratogenicity was generally noted in ratstudies. However, cardiovascular malformations were observed in two studies in ratstreated with doses of 150 mg/kg/d. In mice at doses 70x the clinical dose, cleft palateoccurred at varying incidences (3-30%).

Fertility and reproduction studies have shown that daily doses of 150 to160mg/kg/day to male and female rats caused no adverse effects on the estrous cycle,fertility, parturition, or number and viability of offspring. Plasma levels in rats at150mg/kg/day were 2-fold higher than that observed in humans.

Clarithromycin has been found in the milk of lactating animals.

In 3-day old mice and rats, the LD50 values were approximately half those inadult animals. Juvenile animals presented similar toxicity profiles to matureanimals although enhanced nephrotoxicity in neonatal rats has been reportedin some studies. Slight reductions in erythrocytes, platelets and leukocyteshave also been found in juvenile animals.

Clarithromycin has not been tested for carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Microcrystalline cellulose,
- Croscarmellose sodium,
- Magnesium stearate,
- Colloidal silicon dioxide,
- Polyvinyl pyrrolidone.
- Hydroxypropylcellulose,
- Propylene glycol,
- Titanium dioxide,
- Talc,
- Isopropyl alcohol,
- Methylene chloride

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

6.5 Nature and contents ofcontainer

Presentation: Clarithromycin tablets USP 500 mg (MEDICLAR-500) is available as10 x 7's, 10 x 10's PVC Blister pack.

Primary Container (s):

- Printed blister Foil
- PVC Film clear

Secondary packing:
Such blisters are packed in cartons of GSM 300, made of ITC cyber XL board with aqua varnish.Carton is printed in Multicolor.

Leaflet: leaflet made with 70 GSM Map Lithopaper.

Outer Container:

Such cartons are packed in Export Worthy 5/7 Ply Shippers. These shippers are labelled with product name and relevant batch details and sealed with BOPP tape. Shippers are then strapped with Polypropylene tapes.

Transportation: Should be transported with precautions.

The Cautions Like- This Side Up

- Not For Loose Handling
- Protect from Water
- Avoid Vigorous Transportation Not all pack sizes may be marketed.

6.6 Special precautions for disposal and otherhandling

None

7. MARKETING AUTHORIZATIONHOLDER

Name and Permanent address of the Marketing authorization holder:
Medopharm

"MEDO HOUSE"

25, Puliyur II Main road, Trustpuram, Chennai-600 024, Tamil Nadu, India.

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Manufacturing Site address:
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8. NUMBER (S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

08580/10059/NMR/2022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

10.04.2023

10. DATE OF REVISION OF THE TEXT

12.07.2023