SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Clarem250 mg film-coated tablets
Clarem500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clarem 250 mg film-coated tablets: Each film-coated tablet contains 250 mg clarithromycin.

Clarem 500 mg film-coated tablets: Each film-coated tablet contains 500 mg clarithromycin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Clarem 250 mg film-coated tablets:
Yellow, parallel, capsule shaped, film-coated tablets with Remedica's logo on both sides.

Clarem 500 mgfilm-coated tablets:
Yellow, oval, film-coated tablets, scored on one side and debossedwith "CL500" on the other side.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1Therapeutic indications

Clarithromycin is indicated for the treatment of infections caused by susceptible organisms,in adults and children 12 years of age and older, such as:

- lower respiratory tract infections (see sections 4.4 and 5.1 for Sensitivity Testing) including:
  - bronchitis and
  - community-acquired pneumonia. Combinations of antibiotics (mainly β-lactam with macrolide) are commonly used to treat community-acquired pneumonia. In any case, the national guidelines for the treatment of community-acquired pneumonia must be taken into account.

- upper respiratory tract infections (including rhinosinusitis and pharyngotonsillitis). In particular,it should be used as an alternative treatment in streptococcal pharyngotonsillitis for patients who cannot be given the first-line treatment, which is penicillin. In rheumatic fever, clarithromycin is generally effective in eradicating strep throat. However, at present there are only limited data proving its effectiveness in preventing rheumatic fever.

- skin and soft tissue infections(e.g folliculitis, cellulitis, erysipelas) (see section 4.4 and 5.1 regarding Sensitivity Testing).
- complementary therapy (in combination with other anti-tubercullosis drugs) for the treatment of generalized or localizes infections due to atypical mycobacteria (e.g. *Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium chelonae, Mycobacterium fortuitum* and *Mycobacterium Kansasii*).
- eradication of *Helicobacter Pylori* for the treatment of duodenal ulcers and prevention of it recurrence, if administered in combinations with inhibitors of gastric secretion.
- dental infections, as a drug of second choice.

4.2 Posology and method of administration

Posology

Adults
The usual dose of clarithromycin in adults and children older than 12 years is 250 mg tablet twice daily.In more severe infections, the dosage can be increased to 500mg twice daily. The usual duration of therapy is 5 to 14 days, excluding treatment of community-acquired pneumonia and rhinosinusitis which requires 6 to 14 days.

Dosage in adult patients with mycobacterial infections
Clarithromycin should be used in combination with other antifungal drugs.
The recommended dose for adults is 500 mg twice daily.
In generalized mycobacterial infections in AIDS patients, treatment is continued, as long as clinical microbiological benefit is demonstrated. Clarithromycin should be used in conjunction with other mycobacterial agents.
Treatment of other non-tuberculous mycobacterial infections should continue at the discretion of the physician.

Dosage for eradication of Helicobacter pylori
The recommended dosage regimens are as follows:

Triple therapeutic regimen
Clarithromycin500 mg twice daily in combination with amoxycillin 1000mg twice daily and omeprazole 20 mg twice daily for 7 days.
Clarithromycin500mg twice daily in combination with amoxicillin 1000 mg twice daily and omeprazole 40 mg daily for 7 days.

Double therapeutic regimen
Clarithromycin500 mgthree timesfor 14 days in combination with gastric secretion inhibitors.

Dosage in Dental Infections
250 mg clarithromycin twice daily for 5 days.

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.

Pediatric population
The contents of 250 and 500 mg tablets should not be used in children under 12 years of age.

4.3 Contraindications

Hypersensitivity to macrolide antibiotic drugs or to any of its excipientslisted in section 6.1.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, cisapride, domperidone, pimozideorterfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsade de pointes (see section 4.5).

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).

Clarithromycin should not be given to patients with history of QT prolongation (congenital or document acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (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 with severe hepatic failure in combination with renal impairment.

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).

Concomitant administration with ticagrelor or ranolazine is contraindicated.

Concomitant administration of clarithromycin and lomitapide is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

As with other antibiotics, long-term use may result in colonization with an increased number of non-susceptible bacteria and fungi. If severe infections occur, appropriate treatment should be given.

Clarithromycin should not beprescribed to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy (see section 4.6).

Clarithromycin is principally metabolizedby the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible.

In some instances, hepatic failure with fatal outcome) has been reported(see section 4.8) and generally has been associated with serious underlying diseases and/or concomitant medications. Some patients may have had pre-existing liverdisease or may have alreadytaken other hepatotoxic medicines.. Patients should be advised to discontinuetreatment and contact their physician if signs and symptoms of hepatitis occur, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

The use of any antimicrobial therapy, such as clarithromycin, can be chosen to treat Helicobacter pylori infection for drug-resistant organisms.

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. Clostridium difficile must be considered in all patients who experience diarrhoea following antibiotic use. Detailed 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.

Colchicine:
There have been post-marketing reports of colchicine toxicity whenco-administered with clarithromycin, especially in the elderly and/or patients with renal insufficiency,some of which are fatal (see section 4.5). Concomitant administration of clarithromycin and colchicine is contraindicated (see section 4.3).Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam andintravenous or (oromucosal) midazolam (see section 4.5).

Cardiovascular Events:
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 (see section 4.8). Therefore, as the following conditions may lead to 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 disturbancesor clinically relevant bradycardia.
- patients with electrolyte disturbances such as hypomagnesaemia. Clarithromycin must not be used in patients with hypokalaemia (see section 4.3).

- patients concomitantly taking other medicinal products associated with QT prolongation (see section 4.5).
- concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfenadine is contraindicated (see section 4.3).
- clarithromycin should not be used in patients with congenital or documented acquired QT prolongation or a history of ventricular arrhythmia (see section 4.3).

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

Pneumonia
In view of the emerging resistance of *Streptococcus pneumonia* to macrolides, it is important that sensitivity testing be performed whenprescribing clarithromycin for community-acquired pneumonia. In hospital acquiredpneumonia, clarithromycin should be used in combination withadditional 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 to perform sensitivity tests. 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 *Corynebacteriumminutissimum*, common acne, 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 (see section 4.5).

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

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

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 (see section 4.5).

Oral hypoglycaemic agents/Insulin:
The concomitant use of clarithromycin and oral hypoglycaemic agents (such as sulphonylurias) and/or insulin can result in significant hypoglycaemia. 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 co-administered with warfarin (see section 4.5). INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

Use of any antimicrobial therapy, such as clarithromycin, to treat *H. pylori* infection may select for drug-resistant organisms.

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 be instituted.

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).

Clarem 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 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 (see section 4.3).

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, ventricular fibrillation and torsades de pointes (see section 4.3). 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.

Alkaloids of erysipelas

Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischaemia 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. Concomitant administration of oral midazolam and clarithromycin is contraindicated (see section 4.3).

HMG-CoA Reductase Inhibitors (statins):

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3) as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis.Rhabhdomyoliysis has been reported in patients receivingclarithromycin concomitantly with these statins.Caution is required when prescribing clarithromycin with other statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Caution should be exercised when prescribing clarithromycin with statins. In 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. Patients should be monitored for signs and symptoms of myopathy(see section 4.5).

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

Effects of Other Medicinal Products on Clarithromycin

Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) may induce the metabolism of clarithromycin.

This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inhibitor administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

The following drugs are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dosage adjustment or consideration of alternative treatments may 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 and thus lower the plasma levels of clarithromycin, while increasing those of 14-OH clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

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

Fluconazole:
Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration (C_{min}) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir:
A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. Theclarithromycin C_{max} increased by 31%, C_{min} increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted.

Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should beconsidered: For patients with CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. Forpatients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycingreater than 1 gm/day should not be co-administered with ritonavir.

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

Effect of Clarithromycin on Other Medicinal Products

Direct acting oral anticoagulants (DOACs)
The DOAC dabigatran is a substrate for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolised via CYP3A4 and are also substrates for P-gp. Caution should be exercised when clarithromycin is co-administered with these agents particularly to patients at high risk of bleeding (see section 4.4).

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 co-administration of clarithromycin with these drugs. Serum levels of quinidineand 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 glucoselevels should be monitored during concomitant administration ofclarithromycin and disopyramide.

Oral hypoglycemic agents/Insulin:
With certain hypoglycemic 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.

CYP3A-based interactions:
Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolised by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug.

The use of clarithromycin is contraindicated in patients receiving the CYP3Asubstrate astemizole,cisapride,domperidone, pimozide and terfenadine due to the risk of QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes (see sections 4.3 and 4.4).

The use of clarithromycin is also contraindicated with ergot alkaloids, oral midazolam, HMG CoA reductase inhibitors metabolised mainly by CYP3A4 (e.g. lovastatin and simvastatin), colchicine, ticagrelor and ranolazine (see section 4.3)

Caution is required if clarithromycin is co-administered 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 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.

Drugs or drug classes are known or suspected to be metabolised by the same CYP3A isozyme include (but this list is not comprehensive) alprazolam, carbamazepine, cilostazol, ciclosporin, disopyramide, ibrutinib, methylprednisolone, midazolam (intravenous), omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), quinidine, rifabutin, sildenafil, sirolimus, tacrolimus,, triazolam and vinblastine. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Omeprazole:

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

Sildenafil, tadalafil and vardenafil:
Each of these phosphodiesterase inhibitors is 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 benecessary 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 intravenousadministration of midazolam and 7-fold after oral administration. Concomitantadministration of oral midazolam and clarithromycin should be avoided. Ifintravenous midazolam is co-administered with clarithromycin, the patientmust be closely monitored to allow dose adjustment. The same precautionsshould also apply to other benzodiazepines that are metabolised by CYP3A,including triazolam and alprazolam. For benzodiazepines which are notdependent on CYP3A for their elimination (temazepam, nitrazepam,lorazepam), a clinically important interaction with clarithromycin is unlikely.

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

Other drug interactions

Colchicine:
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 clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by

clarithromycin may lead to increased exposure to colchicine. Concomitant use of clarithromycin and colchicine is contraindicated (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 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 dideoxyinosine. 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 co-administered 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, bradyarrhythmias 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 C_{max} values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are co-administered for a limited time at the doses/formulations studied.

Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see section 4.5).

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embryofoetal development cannot be excluded. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results.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 milkin small amounts. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin.

Fertility
The safety of clarithromycin during breast-feeding has not been confirmed. Clarithromycin is excreted in human milk.

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 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.

The following table displays adverse reactions reported in clinical trials and from post marketing experience with clarithromycin immediate-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 (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and not known (adverse reactions from post-marketing experience; 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.

Undesirable effects reported regarding clarithromycin				
System Organ Class	**Very common ≥1/10**	**Common ≥1/100 to < 1/10**	**Uncommon ≥1/1,000 to < 1/100**	**Not Known* (cannot be estimated from the available data)**
Infections and infestations			Candidiasis,vaginalinfection	Pseudomembranous colitis, erysipelas
Blood and lymphatic system			Leukopenia, neutropenia[4], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders			Hypersensitivity	Anaphylactic reaction. angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety	Psychotic disorder, confusional state[5], depersonalisation, depression,

				disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache	Dizziness, somnolence[5], tremor	Convulsion, ageusia,parosmia, anosmia,paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Electrocardiogram QT prolonged, palpitations	Torsades de pointes, ventricular tachycardia, Ventricular fibrillation
Vascular disorders				Haemorrhage
Gastrointestinal disorders		Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain	Gastritis, stomatitis, glossitis,abdominal Distension[***],constipation, drymouth, eructation, flatulence	Acute pancreatitis Tonguediscolouration, tooth discolouration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis[***], hepatitis[***], alanineaminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransfere increased[***]	Hepatic failure, Jaundicehepatocellular
Skin and subcutaneous tissue disorders		Rash, Hyperhidrosis	Pruritus, urticaria	Severe cutaneous adverse reactions (e.g. acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne
Musculoskeletal and connective tissue disorders				Rhabdomyolysis[2,6] myopathy
Renal and urinary				Renal failure, nephritis interstitial

disorders				
General disorders and administration site conditions			Feeling of misery[***] weakness, chest pain[***] chills[***], fatigue[***]	
Investigations			Blood alkalinephosphataseincreased[***], blood lactatedehydrogenaseincreased[4]	International normalised ratio increased, prothrombin time prolonged, urine colour abnormal

** 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.*
*** In some of the reports of rhabdomyolysis (Side effect reported only in the form of Controlled Release Tablets - included in the SPC of this form), clarithromycin was co-administered with other drugs known to be associated withcolchicine or allopurinol).*
**** Side effects reported in the form of Instant Release Tablets only.*

In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol (see section 4.3 and 4.4).

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 (see section 4.5).

There have been rare reports of clarithromycin ER 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. In several reports, tablet residues have occurred in the context of diarrhoea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g. suspension) or another antibiotic.

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

Paediatric populations
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 shouldusеclarithromycin paediatric suspension.

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

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 2000mg 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 1000mg and 2000mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000mg of clarithromycin.

In these immunocompromised patients, evaluations of laboratory values were made by analysing 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 1000mg or 2000mg 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 4000mg daily for all parameters except White Blood Cell.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

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, hypokalemia and hypoxemia.

Treatment
Adverse reactions accompanying overdosage should be treated by gastric lavage and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use; Macrolides, lincosamides and streptogramins, ATC code: J01FA09

Clarithromycin is a semi-synthetic macrolide antibiotic, a substituent of the hydroxyl group at position 6 with $CH_3$0group in the lactone ring of erythromycin. Clarithromycin in particular is 6-O-methylerythromycin A. It is a white, odorless, bitter powder, insoluble in water and soluble in ethanol, methanol and acetonitrile. The molecular weight is 747.96.

Microbiology
Clarithromycinexerts its antibacterial activity by binding to the 5OS ribosomal sub-unit of susceptible bacteria,thereby inhibits their protein synthesis.

Clarithromycin has been shown to have excellent *in vitro* activity against both reference bacterial strains and those isolated in clinical practice. It is very active against a wide variety of aerobic and anaerobic Gram-positive and Gram-negative microorganisms. Clarithromycin minimum inhibitory concentrations (MICs) are usually one log2 more active than erythromycin MICs.

Laboratory (*in vitro*) data also show that clarithromycin has excellent action against *Legionella pneumophila* and *Mycoplasma pneumoniae*. *In vitro* and *in vivo* data indicate that clarithromycin is active against clinically important mycobacterial strains.

It has bactericidal activity against *Helicobacter pylori* and this action is stronger at neutral pH than at acidic. *In vitro* data indicate that *Enterobacteriaceae and Pseudomonas* strains as well as other non-fermenting Gram lactose negatives are not sensitive to clarithromycin.

Clarithromycin has been shown to be effective against most strains of the following microorganisms *in vitro* and in clinical infections as described in section 4.1:

Aerobic Gram-positive microorganisms:
Staphylococcus aureus (methicillin susceptible)
Streptococcus pneumoniae
Streptococcus pyogenes
Listeria monocytogenes

Aerobic Gram-negative microorganisms:
Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
Legionella pneumophila
Other Microorganisms:
Mycoplasma pneumoniae
Chlamydia pneumonia (TWAR)
Chlamydia trachomatis

Mycoplasma:
Mycobacterium chelonar
Mycobacterium fortuitum
Mycobacterium aviumcomplex (MAC) which consists of:

- *Mycobacterium avium*
- *Mycobacterium intracellulare*

Mycobacterium leprae
Mycobacterum kansasii; Mycoplasmapneumoniae; Ureaplasmaurealyticum.

B-lactamase production does not appear to affect clarithromycin activity.

NOTE: Most staphylococcal strains that are resistant to methicillin and oxacillin are also resistant to clarithromycin.

Helicobacter:
Helicobacter pylori

In pre-treatment cultures, *H. pylori* was isolated and MIC's of clarithromycin were determined prior to treatment in 104 patients. Of these, four patients had resistant strains, two patients had intermediate susceptibility strains, and 98 patients had susceptible strains.

The following *in vitro* data are available, but their clinical significance is unknown. Clarithromycin shows *in vitro* activity against most strains of the following microorganisms. However, the safety and efficacy of clarithromycin in the treatment of clinical infections due to these microorganisms have not yet been demonstrated by appropriate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms:
Streptococcus agalactiae
Streptococci (Group C, F, G)
Viridans group streptococci

Aerobic Gram-Negative Microorganisms:
Bordetella pertussis
Pasteurella multocida

Anaerobic Gram-Positive Microorganisms:
Clostridium perfringens
Peptococcus niger
Propionibacterium acnes

Anaerobic Gram-Negative Microorganisms:
Bacteroides melaninogenicus

Spirochetes:
Borrelia burgdorferi
Treponema pallidum
Campylobacters
Campylobacter jejuni

The majormetabolite of clarithromycin in humans and monkeys is a bactericidal active metabolite,14-OH-clarithromycin.This metabolite is equally active or 1-2 times less active than the parent substance for most microorganisms, while in H. influenzae it is twice as

active. The parent substance and the14-OH-metabolite exert either cumulative or synergistic activity in vitro and *in vivo* in *H. influenza* depending on the bacterial strains.

Clarithromycin was shown to be 2-10 times more effective than erythromycin in experimental animal models. It has been shown, for example, to be more effective than erythromycin in systemic mouse infection, subcutaneous mouse abscess, and mouse respiratory infections due to *S. pneumoniae, S. aureus, S. pyogenes*, and H. influenzae. This activity was more evident in guinea pigs with Legionella infection. An intraperitoneal dose of clarithromycin 1.6 mg / kg / day was more active than 50 mg / kg / day erythromycin.

Sensitivity test
Quantitative methods that require measurements of band diameter give the most accurate estimate of the susceptibility of bacteria to antimicrobial derivatives. A method using discs impregnated with 15mcg clarithromycin is recommendedfor sensitivity tests (Kirby-Bauer diffusion test). Interpretations correlate the diameters of the sensory disc inhibition zones with the MIC values of clarithromycin. MICs are determined based on meat and agar broth solubilization methods.

With this method, the labeling of the laboratory as "sensitive" means that the pathogen is likely to respond to treatment. The designation "resistant" means that the pathogen is not considered likely to respond to treatment. The designation "moderately sensitive" (or intermediate) means that the therapeutic effect of the drug may be questionable or that the microorganism could be sensitive to higher doses. It is sensitive when the MIC is <2 μg / ml of the drug and resistant when the MIC is> 8 μg / ml.

Clinical studies

Helicobacter pylori is closely related to peptic ulcer. In duodenal ulcer, *H. pylori* infection accounts for 90%. Eradication of *Helicobacter pylori* significantly reduces the incidence of recurrence of duodenal ulcer and the need for long-term antisecretory therapy.

Triple treatment regimen in duodenal ulcer
In a completely controlled double-blind study, patients with duodenal ulcer with confirmed *H. pylori* infection received eradication treatment with clarithromycin 500 mg twice daily, in combination with amoxicillin 1000 mg twice daily and omeprazole 20 mg daily or 20 mg daily. 2 times a day for 10 days or for 7 days or clarithromycin 500 mg 3 times a day in combination with omeprazole 40 mg daily for 14 days. Eradication of *H. pylori* was achieved in 90% of patients receiving triple therapy versus 60% of patients receiving dual therapy.

In an independent study, patients with *H. pylori* infection received eradication therapy with clarithromycin 500 mg twice daily in combination with amoxicillin 1000 mg twice daily and omeprazole 20 mg daily (group A) or omeprazole 20 mg twice daily. day (Group B) for seven days. In patients who had not previously received treatment for *H. pylori*, eradication of *H. pylori* was observed in 86% (95% CI = 69-95) in group A and 75% (95% CI = 62 to 85) in group B, without the difference being statistically significant.

In an open-label study of *H. pylori*, patients with duodenal ulcer or non-ulcerative indigestion (NUD) received eradication therapy with clarithromycin 500 mg twice daily, lansoprazole 30

mg twice daily in combination with amoxicillin 1000 mg twice daily for ten days. In an analysis of all treated patients *H. pylori* was eradicated in 91% of patients.

Double therapeutic regimen
In 4 well-controlled double-blind studies, patients with duodenal ulcer with confirmed *H. pylori* infection received eradication treatment with clarithromycin 500 mg 3 times daily in combination with omeprazole 40 mg daily for 14 days followed by omeprazole 40 mg (study A). 20 mg per day (studies B, C & D) for an additional 14 days. In each control group, patients received only omeprazole for 28 days. Study A found eradication of *H. pylori* in more than 80% of patients receiving clarithromycin with omeprazole and only 1% of patients receiving omeprazole alone. In studies B, C & D, the mean eradication rate was greater than 70% (clinically evaluable analysis) in patients receiving clarithromycin in combination with omeprazole, and less than 1% in patients receiving omeprazole alone. In each study, the recurrence rate of patients at 6 months after treatment was significantly lower in the clarithromycin and omeprazole patient groups compared with the omeprazole alone groups.

In a study blind to the researcher, patients with *H. pylori* infection received eradication treatment with clarithromycin 500 mg three times daily in combination with lansoprazole 60 mg / day in single or divided doses for 14 days. The combined eradication rate was over 60%.

Other treatment regimens for Helicobacter pylori eradication
Clarithromycin has been used in other treatment regimens to eradicate *H. pylori*, such as:
- Clarithromycin with bismuth subsalicylate and ranitidine.
- Clarithromycin with metronidazole and omeprazole or lansoprazole.

Research is ongoing with other active ingredients in combination with clarithromycin.

5.2 Pharmacokinetic properties

Absorption
The pharmacokinetics of oral clarithromycin have been extensively studied in various animal species and adults and have been shown to be non-linear. These studies have shown that clarithromycin is easily and rapidly absorbed with an absolute bioavailability of 50%. No accumulation or alteration of its metabolism was observed in any species of animals during multiple administrations. Taking food shortly before administration increases the bioavailability of clarithromycin by 25%. Ultimately, this increase is negligible and should be of little clinical significance as long as clarithromycin is administered in the recommended dosing regimens. Thus, clarithromycin could be administered either in the presence or absence of food.

Distribution, Biotransformation and Abortion
In vitro
In vitro studies have shown that clarithromycin is approximately 70% bound to plasma proteins in humans at therapeutic concentrations of 0.45 to 4.5 mcg / ml. The reduction of its binding to 41% for concentrations of 45.0 mcg / ml is probably interpreted as saturation of the binding pointsbut, this phenomenon was observed only at concentrations of clarithromycin much higher than the therapeutic levels of the drug.

In vivo

The results of animal studies showed that clarithromycin levels in all tissues except the central nervous system were multiples of circulating drug levels. The highest concentrations were observed mainly in the liver and lung where the ratio of tissue to plasma (I / P) reached 10 to 20.

Healthy volunteers
At 250 mg twice daily, peak steady-state plasma concentrations of clarithromycin are reached after 2-3 days and average 1 mcg / ml for clarithromycin and 0.6 mcg / ml for 14-OH-clarithromycin. The biological half-life for the parent substance and the metabolite is 3-4 hours and 5-6 hours, respectively. At 500 mg twice daily, the steady state C_{max} of clarithromycin and 14-OH-clarithromycin were achieved with the fifth dose. After the fifth and seventh doses the steady state C_{max} of clarithromycin and 14-OH-clarithromycin are in the range of 2.7 to 2.9 mcg / ml and 0.88 to 0.83 mcg / ml respectively. At this dosage, the half-life of the parent substance is 4.5 to 4.8 hours and that of 14-OH-clarithromycin is 6.9 to 8.7 hours. At steady state, 14-OH-clarithromycin levels do not increase proportionally with increasing dosing of clarithromycin while the apparent half-life of both clarithromycin and its hydroxylated metabolite shows an increasing trend at higher doses. This non-linear pharmacokinetic behavior of clarithromycin in combination with the general reduction in the formation of 14-hydroxylation and N-demethylation products in higher doses indicate that clarithromycin metabolism is saturated at these high doses.

When administered as monotherapy at a dose of 1500 mg daily in three doses, clarithromycin showed a steady state, a mean C_{max} and C_{min} higher by 31% and 119%, respectively, compared with the values observed for the 1000 mg dose per day in two doses studied in previous studies. Also, $AUC0_{-24}$ was 65% higher with the dose of 1500 mg in three doses compared to the dose of 1000 mg in two doses. No significant change in T_{max} and half-life of clarithromycin was observed at the dose of 1500 mg per day in three doses compared to the dose of 1000 mg per day in two doses.

Following single oral doses of 250 mg or 1200 mg in adults, urinary clarithromycin is 37.9% of the lowest dose and 46.0% of the higher dose. Excretion of clarithromycin from the stool is 40.2% and 29.1% (including a patient with only one stool sample containing 14.1%), respectively.

Patients
Clarithromycin and its 14-OH-metabolite are widely distributed in tissues and body fluids. Limited data from a small number of patients showed that, after per os administration, clarithromycin did not achieve significant cerebrospinal fluid concentrations (in patients with normal blood-brain barrier, clarithromycin concentrations ranged from 1 to 2% of the corresponding plasma). Tissue concentrations are usually multiples of serum concentrations. Examples of corresponding tissue and serum concentrations are given below:

CONCENTRATION after 250 mg every 12 hours		
Tissue	Tissue (mcg /ml)	Serum (mcg /ml)
Tonsil	1,6	0,8
Lung	8,8	1,7

Liver failure

One study compared a group of healthy volunteers with a group of patients with hepatic impairment at a dose of 250 mg twice daily for 2 days and an additional dose on the third day. Steady-state plasma levels and general clarithromycin clearance showed no significant differences between the two groups. In contrast, steady-state 14-OH-metabolite concentrations were significantly lower in the group of patients with hepatic impairment. The decrease in the 14-hydroxylation of the parent substance was partially offset by a corresponding increase in the renal clearance of the latter, resulting in similar steady-state clarithromycin levels observed in patients with hepatic impairment compared with healthy volunteers. These results indicate that no dose adjustment is required in individuals with moderate or severe hepatic impairment as long as their renal function is normal.

Renal failure
A multi-dose study with 500 mg clarithromycin tablets was also performed to evaluate and compare the pharmacokinetic behavior of the drug in patients with intact renal function and in patients with renal insufficiency. Plasma levels, half-lives, C_{max} and C_{min} as well as AUCs of both clarithromycin and 14-OH-metabolite increased in patients with renal insufficiency. Clearance and excretion of potassium in the urine decreased. The difference in these parameters was proportional to the degree of renal impairment. The more severe the renal insufficiency, the greater the difference (see sections 4.2 and 4.3).

Elderly people
A study was also performed to evaluate and compare the safety and pharmacokinetics of clarithromycin in multiple doses of 500 mg orally in older men and women versus young healthy males. In the elderly group, plasma levels were higher and miscarriage slower than in the younger group, for both the parent drug and the 14-OH-metabolite. However, there was no difference between the two groups when renal clearance of the drug was correlated with creatinine clearance values. From these results it is concluded that the administration of clarithromycin is modified only according to the renal function of the patients and not according to their age itself.

Infections by Mycobacterium avium
The steady-state concentrations of clarithromycin in the blood and the 14-OH-metabolite observed after dosing 1000 mg daily in two doses in adult patients with HIV infections were similar to those observed in healthy volunteers.However, at the highest doses that may be required to treat atypical mycobacterial infections, clarithromycin concentrations were much higher than those observed at standard doses. In adult patients with HIV infections and in steady state, C_{max} values ranged between 2 and 4 mcg / ml, and 5 to 10 mcg / ml at the respective doses of clarithromycin 1000 and 2000 mg daily in two doses. The half-life was increased at these higher doses compared to the usual doses in healthy subjects. The higher plasma concentrations and the longer half-life of clarithromycin observed at these doses are consistent with the known non-linear pharmacokinetic behavior of clarithromycin.

Co-administration with omeprazole
A study was performed with clarithromycin at a dose of 500 mg 3 times daily in combination with omeprazole 40 mg once daily. When clarithromycin was administered as monotherapy at a dose of 500 mg 3 times daily and at steady state, the mean values of C_{max} and C_{min} were 3.8 μg / ml and 1.8 μg / ml, respectively. Also, the mean values of AUC 0-8 of clarithromycin were 22.9 μg / h / ml, T_{max} and half-life were 2.1h and 5.3h respectively.

In the same study, when clarithromycin 500 mg was administered 3 times daily in combination with omeprazole at a dose of 40 mg once daily, an increase in the half-life and AUC0-24 of omeprazole was observed. In all volunteers, the mean AUC0-24 of omeprazole increased by 89% and its mean half-life by 34% during concomitant administration of clarithromycin compared with omeprazole alone. When administered with omeprazole at steady state, C_{max}, $C_{min}$and AUC0-8 of clarithromycin increased by 10%, 27%, and 15%, respectively, compared with placebo values of clarithromycin.

At steady state, the concentrations of clarithromycin in gastric mucus 6 hours after administration were 25-fold higher in the clarithromycin-omeprazole treatment group compared with the clarithromycin group alone. 6 hours after administration, mean clarithromycin concentrations in gastric tissue were 2-fold higher with concomitant clarithromycin and omeprazole compared with placebo clarithromycin.

5.3 Preclinical safety data

Acute, medium and chronic toxicity
Studies have been performed in mice, rats, dogs and/or monkeyswith oral clarithromycin. The duration of administration ranged from a single dose to repeated daily administrations for 6 consecutive months.

Acute toxicity studies in mice and rats showed a case of death of a rat but no death in mice upon oral administration of 5 g / kg / BW. Therefore, the mean lethal dose was above 5 g / kg which is the maximum dose that can be administered.

No adverse effects were attributed to clarithromycin in monkeys receiving 100 mg / kg per day for 14 consecutive days or 35 mg / kg per day for 1 month. No adverse effects were also observed in rats receiving 75 mg / kg per day for 1 month, 35 mg / kg per day for 3 months or 8 mg / kg per day for 6 months. Dogs were more sensitive to clarithromycin. They tolerated 50 mg / kg per day for 14 days, 10 mg / kg per day for 1 and 3 months and 4 mg / kg per day for 6 months without adverse effects.

At toxic doses, the main clinical signs observed in these studies were: vomiting, weakness, decreased food intake and weight gain, salivation, dehydration and hyperactivity. Two of the 10 monkeys given 400 mg / kg per day died on day 8 of treatment. Some of the monkeys that survived after administration of 400 mg / kg per day for 28 days experienced yellow stools in a few isolated cases.

The main target organ in toxic doses in all species of experimental animals was the liver. Hepatotoxicity in all species was found with premature increases in serum alkaline phosphatase, alanine and aspartate aminotransferase, gamma-glutamyltransferase, and / or lactic dehydrogenase concentrations. Discontinuation of the drug led to a return to normal values of these specific parameters.

Other organs affected but less common in the various studies were the stomach, thymus and other lymphoid tissues, as well as the kidneys. Conjunctivitis and tearing were observed only in dogs after almost therapeutic doses. At mass doses of 400 mg / kg per day, some dogs and monkeys showed turbidity and / or corneal edema.

Fertility, reproduction and teratogenicity
Fertility and reproduction studies showed that daily doses of 150-160 mg / kg in male and female rats had no adverse effects on the reproductive cycle, fertility, parturition, number and viability of offspring. Two teratogenicity studies in Wistar (oral) and Sprague-Dawley (oral and intravenous) rats, one study in New Zealand with rabbits and one study in canine monkeys showed that clarithromycin had no effect. Only in a complementary study in Sprague-Dawley rats with similar doses and substantially similar conditions was a very small, statistically insignificant incidence (approximately 6%) of cardiovascular abnormalities observed. These abnormalities were thought to be due to independent expression of genetic changes in the colony. Two studies in mice showed a variable incidence of lycostoma (3-30%) after doses 70 times higher than the maximum usual therapeutic doses in humans (500 mg 2 times daily). However, these abnormalities were not found at doses 35 times higher than the maximum doses recommended in humans, which means that they are toxic to the mother and fetus rather than teratogenic.

It has been shown that in monkeys, clarithromycin can cause fetal loss when administered from the 20th day of pregnancy, at about ten times the maximum standard therapeutic dose administered to humans. This phenomenon has been attributed to the toxicity of very high doses of the drug to the mother. An additional study in pregnant monkeys at doses 2.5 to 5 times the maximum usual daily dose showed no specific risk to the fetus.

The lethal potential test in mice at 1000 mg / kg per day (approximately 70 times the maximum clinical daily dose in humans) was clearly negative for mutagenicity, and a Section 1 study in rats receiving up to 500 mg / kg per day (approximately 35 times the maximum therapeutic daily dose in humans) for 80 days, did not show functional infertility in male animals exposed to this prolonged administration of very high doses of clarithromycin.

Mutagenesis
Studies to evaluate the mutagenic potential of clarithromycin were performed in both inactivated and activated rat liver mitochondria (Ames Test). The results of these studies did not show mutagenic potential at drug concentrations up to a maximum of 25 mcg per plate. At a concentration of 50 mcg, the drug was toxic to all strains tested.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Povidone
Cellulose,microcrystalline
Sodium starch glycolate (Type A)
Silicon, colloidal anhydrous
Magnesium Stearate

Coating
Hypromellose
Macrogol 400
Titanium Dioxide

Talc
Quinoline Yellow aluminium lake E104
Orange Liquid

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30 ℃.

6.5 Nature and contents of container

Clarem 250 mg film-coated tablets:
Cardboard box containing Aluminium-PVC/PE/PVDC blisters of 7 film-coated tablets.
Pack size of 70film-coated tablets.

Clarem 500 mgfilm-coated tablets:
CardboardboxcontainingAluminium-PVC/PE/PVDC blisters of 7 film-coatedtablets.
Pack size of 14film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd
Aharnon Str., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING ATHORISATION NUMBER (S)

Clarem 250 mg film-coated tablets: 06625/08178/REN/2021
Clarem 500 mgfilm-coated tablets: 06757/08176/REN/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Clarem 250 mg film-coated tablets:

Date of first authorization: 30 October 2008
Date of latest renewal: 19 October 2021

Clarem 500 mgfilm-coated tablets:
Date of first authorization: 11 August 2005
Date of latest renewal: 04 November 2021

10. DATE OF REVISION OF THE TEXT

14/07/2023

For internal use only: et-spc-clarem-fc-tabs-v02-r01-a0