SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEKLARIT 500 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Clarithromycin..500 mg

Excipients:
Croscarmellose sodium..............................70 mg
Tartrazine...0.92 mg
For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film Coated Tablet.
Yellow film-coated, homogenous, oblong tablets scored in the middle on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DEKLARIT Film Coated Tablets are indicated in adults and adolescents of 12 years and older for the treatment of the following mild to moderate infections caused by susceptible organisms:

1) Upper respiratory tract infections: Pharyngitis/tonsillitis caused by *Streptococcus pyogenes*, acute maxillary sinusitis caused by *Haemophilus influenzae, Moraxella catarrhalis* or *Streptococcus pneumonia.*
2) Lower respiratory tract infections: Acute bacterial exacerbations of chronic bronchitis caused by *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis* or *Streptococcus pneumoniae*; community-acquired pneumonia caused by *Haemophilus influenzae, Mycoplasma pneumoniae, Streptococcus pneumoniae* or *Chlamydia pneumoniae* (TWAR).
3) Skin and soft tissue infections: Uncomplicated skin and soft tissue infections caused by *Staphylococcus aureus* or *Streptococcus pyogenes.* Abscesses usually require surgical drainage.
4) Disseminated or localized mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare* and localized infections due to *Mycobacterium chelonae, Mycobacterium fortuitum* and *Mycobacterium kansasii.*
5) Prophylaxis of disseminated *Mycobacterium avium* complex (MAC) infections in HIV-infected patients with CD4 lymphocyte count ≤100/ mm^3.
6) Eradication of *H. pylori* to reduce the recurrence of duodenal ulcer in the presence of acid suppression.

4.2 Posology and method of administration
Posology:

Dose Guide for Adults

INFECTION	**One dose every 12 hours**	**Usual Duration (days)**
Upper respiratory tract infections	250 mg 500 mg in severe infections	6 - 14
– Pharyngitis/tonsillitis – Acute maxillary sinusitis	250 mg 500 mg in severe infections	6 - 14
Lower respiratory tract infections	250 mg 500 mg in severe infections	6 - 14
Acute exacerbations of chronic bronchitis caused by following strains		
– *S. pneumoniae* – *M. catarrhalis* – *H. influenzae*	250 mg 250 mg 500 mg	7 - 14 7 - 14 7 - 14
Pneumonia caused by the following		
– *S. pneumoniae* – *M. pneumoniae*	250 mg 250 mg	7 - 14 7 - 14
Uncomplicated skin and soft tissue infections	250 mg	6 - 14

Mycobacterial infections: In adult patients with mycobacterial infection, recommended starting dose is 500 mg twice daily. If clinical or bacteriological response cannot be achieved within 3 to 4 weeks, dose can be increased to 1000 mg twice daily. For treatment of disseminated MAC infections, treatment should be continued until desired clinical and microbiological result is obtained. Clarithromycin should be administered in combination with other antimycobacterial medicines.

In other nontuberculous mycobacterial infections, duration of therapy has to be determined by the physician.

MAC prophylaxis: The recommended dosage of clarithromycin in adults is 500 mg twice daily.

Dose for *H. pylori* eradication: Following dose regimens are recommended for *H. pylori* eradication:

Triple therapy regimen:
500 mg clarithromycin twice daily is co-administered with 1000 mg amoxicillin twice daily and 30 mg lansoprazole twice daily for 10 days.
500 mg clarithromycin twice daily is co-administered with 1000 mg amoxicillin twice daily and 20 mg omeprazole twice daily for 10 days.

Frequency and duration of administration:
The usual duration of therapy is 7 to 14 days, excluding treatment of upper respiratory tract infections and uncomplicated skin and soft tissue infections which require 6 to 14 days of therapy.

Method of administration:
Tablets should be swallowed irrespective of food intake and at the same time each day.

Additional information on special populations
Renal impairment:
Dose adjustment is not necessary for patients with moderate renal insufficiency (creatinine clearance 30-60 ml/minute).

In patients with severe renal insufficiency (creatinine clearance <30 ml/ minute), daily dose should be reduced by half. Daily maximum dose is 500 mg for patients with severe renal insufficiency.

In dosage reductions resulting in less than 500 mg/daily, other Clarithromycin formulations (for example Clarithromycin oral suspensions) should be preferred. Treatment should not be continued for more than 14 days in these patients.

Hepatic impairment:
DEKLARIT should be administered with caution to patients with hepatic impairment.

Pediatric population:
No clinical trials have been conducted with clarithromycin 500 mg tablets in children under 12 years of age and is therefore not recommended. Clarithromycin suspension forms are available for children under 12 years of age.

Geriatric population:
Dose adjustment should be considered in elderly patients with severe renal impairment.

4.3 Contraindications
DEKLARIT is contraindicated in patients with known hypersensitivity to macrolide antibiotic drugs or any of its excipients listed in section 6.1.

Concomitant administration of clarithromycin with the following medicines is contraindicated: Astemizole, cisapride, pimozide and terfenadine as this may cause in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation and torsades de pointes.

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

Concomitant administration of clarithromycin with oral midazolam is contraindicated.

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

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

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

As with other strong CYP3A4 inhibitors, clarithromycin is contraindicated in patients with renal or hepatic impairment taking colchicine (see sections 4.4 and 4.5).

4.4 Special warning and precautions for use
Administration of any anti-microbial treatment such as Clarithromycin for treatment of *H. pylori* infection may cause increase in organisms resistant to the medicine.

Clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking this drug, the patient should be apprised of the potential hazard to the fetus. Clarithromycin has demonstrated adverse effects of pregnancy outcome and/or embryo-fetal development in monkeys, rats, mice, and rabbits at doses that produced plasma levels 2 to 17 times the serum levels achieved in humans treated at the maximum recommended human doses (see section 4.6).

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

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

In one clinical trial evaluating treatment with Clarithromycin on outcomes in patients with coronary artery disease, an increase in risk of all-cause mortality one year or more after the end of treatment was observed in patients randomized to receive Clarithromycin. Clarithromycin for treatment of coronary artery disease is not an approved indication. The cause of the increased risk has not been established. Other epidemiologic studies evaluating this risk have shown variable results. Consider balancing this potential risk with the treatment benefits when prescribing Clarithromycin in patients who have suspected or confirmed coronary artery disease.

Due to the risk for QT prolongation, clarithromycin should be used with caution in patients with coronary artery disease, severe cardiac insufficiency, hypomagnesaemia, bradycardia (<50 bpm), or when co-administered with other medicinal products associated with a QT prolongation (see section 4.5)

Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).

Pseudomembranous colitis
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including clarithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*.

CDAD should be taken into consideration in all patients with diarrhea which develops after antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of Clostridium. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Exacerbation of symptoms of myasthenia gravis has been reported in patients receiving clarithromycin therapy.

Renal and hepatic impairment
Clarithromycin is principally metabolized by the liver. Therefore, caution should be exercised in administering this antibiotic to patients with impaired hepatic function. Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Clarithromycin should be immediately stopped if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Caution should be exercised when administering clarithromycin to patients with moderate to severe renal impairment. In addition to this, in the presence of severe renal impairment, decreased dosage or prolonged dosing intervals may be appropriate whether there is hepatic insufficiency or not.

Colchicine toxicity
There have been reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see section 4.5). If concomitant administration of colchicine and clarithromycin is necessary, patients should be monitored for clinical symptoms of colchicine toxicity. The dose of colchicine should be reduced when co-administered with clarithromycin in all patients. Concomitant use of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment (see section 4.3).

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

Caution is advised regarding concomitant administration of clarithromycin with other ototoxic medicines, especially with aminoglycosides. Monitoring of vestibular and auditory function should be carried out during and after treatment.

Oral hypoglycemic agents/Insulin
The concomitant use of clarithromycin and oral hypoglycemic agents and/or insulin can result in significant hypoglycemia. With certain hypoglycemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and

could cause hypoglycemia when used concomitantly. Careful monitoring of glucose is recommended.

Oral anticoagulants
There is a risk of serious hemorrhage and significant elevations in INR and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

HMG-CoA reductase inhibitors (statins)
Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis (see section 4.3). Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. Patients should be monitored for signs and symptoms of myopathy. 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.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see section 4.5).

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

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

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome, toxic epidermal necrolysis, DRESS, and Henoch-Schonlein purpura, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Sodium
Each film coated tablet of DEKLARIT contains 6.68 mg sodium, to be taken into consideration for patients on a controlled sodium diet.

Tartrazine
Each film coated tablet of DEKLARIT contains 0.92 mg tartrazine. It may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

The use of the following drugs is contraindicated due to the potential for severe drug interaction.

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 a 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.

Ergot alkaloids:
Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated (see section 4.3).

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.

Effects of other medicinal products on clarithromycin

CYP3A inducers:
Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carabamazepin, phenobarbital, St. Johns Wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to a reduced efficacy. Furthermore it might be necessary to monitor the plasma levels of the CYP3A4 inducer, which could be increased owing to the inhibition of CYP3A4 by clarithromycin (see also the relevant product information for the CYP3A4 inducer 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(R)-hydroxy-clarithromycin (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.

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.

Fluconazole 200 mg/day was administered concomitantly with clarithromycin 500 mg/day twice daily to 21 healthy volunteers. The mean steady-state minimum concentration (C_{min}) and area under the curve (AUC) of clarithromycin were measured as 33% and 18%, respectively. Steady-state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No dose adjustment of clarithromycin is necessary.

Ritonavir:
A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every 8 hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin 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[R]-hydroxyclarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CL_{CR} 30 to 60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} <30 ml/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 g/day should not be coadministered with ritonavir (see section 4.2).

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

Effects of clarithromycin on other medicinal products

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

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

primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin. The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isozyme:
Alfentanil, bromocriptine, alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam, vinblastine, phenytoin, hexobarbital, theophylline and valproate but this list is not exhaustive.

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.

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.

Ranitidine bismuth citrate
Although these effects are clinically insignificant, co-administration of clarithromycin with ranitidin bismutht citrate resulted in increased in plasma concentrations of ranitidine, bismuth and 14-hydroxyclarithromycin.

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

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

Triazolobenzodiazepines (e.g. alprazolam, midazolam, triazolam)
When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. Drug delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the drug, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam,

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

Other drug interactions

Colchicine
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. Patients should be monitored for clinical symptoms of colchicine toxicity. When colchicines are co-administered with clarithromycin in patients with normal renal and hepatic function, colchicine dose should be reduced. Co-administration of colchicines and clarithromycin is contraindicated in patients with renal or hepatic insufficiency (see sections 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 pediatric 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 metabolized by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.

There are no in-vivo human data available describing an interaction between clarithromycin and the following drugs: aprepitant, eletriptan, halofantrine and ziprasidone. However, because in vitro data suggest these drugs are CYP3A substrates, caution should be used when they are co-administered with clarithromycin. Eletriptan should not be co-administered with CYP3A inhibitors such as clarithromycin.

There have been spontaneous or published reports of drug interactions of CYP3A inhibitors, including clarithromycin, with cyclosporine, tacrolimus, methylprednisolone, vinblastine and cilostazol.

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 3 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 4.4).

Didanosine
Simultaneous administration of clarithromycin tablets and didanosine to HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.

4.6 Fertility, pregnancy and lactation
General Recommendation
Pregnancy category is C.

Women of child-bearing potential/Contraception
No available data.

Pregnancy
The safety of clarithromycin for use during pregnancy has not been established. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

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

Fertility
Fertility and reproduction studies have shown that daily doses of up to 150-160 mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring (see section 5.3).

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 pediatric populations are abdominal pain, diarrhea, 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 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.

Adverse Reactions Reported with Clarithromycin

System Organ Class	**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, vaginal infection	Pseudomembranous colitis, erysipelas, erythrasma
Blood and		Leukopenia, neutropenia,	Agranulocytosis,

lymphatic system		eosinophilia	thrombocytopenia
Immune system disorders		Hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders		Anorexia, decreased appetite	Hypoglycemia
Psychiatric disorders	Insomnia	Anxiety	Psychotic disorder, confusional state, depersonalization, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders	Dysgeusia, headache, taste perversion	Dizziness, tremor	Convulsion, ageusia, parosmia, anosmia, paresthesia
Ear and labyrinth disorders		Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders		Electrocardiogram QT prolonged, palpitations	Torsade de pointes, ventricular tachycardia
Vascular disorders			Hemorrhage
Gastrointestinal disorders	Diarrhea, vomiting, dyspepsia, nausea, abdominal pain	Gastritis, stomatitis, glossitis, abdominal distension, constipation, dry mouth, eructation, flatulence	Pancreatitis acute, tongue discoloration, tooth discoloration
Hepatobiliary disorders	Liver function test abnormal	Cholestasis, hepatitis, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders	Rash, hyperhidrosis	Pruritus, urticaria	Severe cutaneous adverse reactions (SCAR) (e.g. Acute generalized exanthematous pustulosis (AGEP),Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS)),acne, Henoch-Schonlein purpura
Musculoskeletal and connective tissue disorders			Myopathy
Renal and urinary disorders			Renal failure, nephritis interstitial
General disorders and administration site conditions		Malaise, asthenia, chest pain, chills, fatigue	
Investigations		Blood alkaline phosphatase increased, blood lactate dehydrogenase increased	International normalized ratio increased, prothrombin time prolonged, urine color 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.

There have been reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see sections 4.4 and 4.5).

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 HIV disease or intercurrent illness.

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

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

Changes in Laboratory Values
Changes in laboratory values with possible clinical significance were as follows:
Hepatic: elevated SGPT (ALT) <1%; SGOT (AST) <1%; GGT <1%; alkaline phosphatase <1%; LDH <1%; total bilirubin <1%
Hematologic: decreased WBC <1%; elevated prothrombin time 1%
Renal: elevated BUN 4%; elevated serum creatinine <1%

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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
Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behavior, hypokalemia and hypoxemia.
Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use – Macrolides
ATC code: J01FA09

DEKLARIT (Clarithromycin) is a semi-synthetic macrolide antibiotic.
Its chemical name is 6-0-methylerythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. The 14-OH metabolite of clarithromycin also has a clinically significant antimicrobial activity.

Microbiology
Clarithromycin has demonstrated excellent *in vitro* activity against both standard strains of bacteria and clinical isolates. It is highly potent against a wide variety of aerobic and anaerobic Gram-positive and Gram-negative organisms. The minimum inhibitory concentrations (MIC) of clarithromycin are generally one $\log_2$ dilution more potent than the MIC of erythromycin.

In vitro data also indicate clarithromycin has excellent activity against *Legionella pneumophilia*, and *Mycoplasma pneumonia*. It is also effective on *Mycobacterium avium* complex (MAC) microorganisms. It exerts bactericide effect against *Helicobacter pylori*. This effect of Clarithromycin is higher with neutral pH compared to acid pH.
The *in vitro* and *in vivo* data show that this antibiotic has activity against clinically significant mycobacterial species. *In vitro* data indicate *Enterobacteriaceae*, pseudomonas species and other non-lactose fermenting Gram negative bacilli are not sensitive to clarithromycin.

Clarithromycin has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections (see sections 4.1 and 4.2):
Gram positive aerobes: *Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Listeria monocytogenes.*
Gram negative aerobes: *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, Legionella pneumophila,*
Other aerobes: *Mycoplasma pneumoniae, Chlamydia pneumoniae (TWAR)*
Mycobacteria: *Mycobacterium leprae, Mycobacterium kansasii, Mycobacterium chelonae, Mycobacterium fortuitum, Mycobacterium avium complex (MAC): Mycobacterium avium and Mycobacterium intracellulare*
Beta lactamase production does not have effect on Clarithromycin activity.

NOTE: Most strains of methicillin-resistant and oxacillin-resistant staphylococcus are resistant to Clarithromycin.

Helicobacter pylori
Helicobacter pylori is strongly associated with peptic ulcer disease. 90% to 100% of patients with duodenal ulcer are infected with this pathogen. Eradication of *H. pylori* has been shown to reduce the rate of duodenal ulcer recurrence, thereby reducing the need for maintenance anti-secretory therapy.

Clarithromycin exhibits *in vitro* activity against most strains of the following microorganisms; however, the safety and effectiveness of clarithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram positive aerobes; *Streptococcus agalactiae, Streptococci (Group C.F.G), Viridians group streptococci*
Gram negative aerobes; *Bordetella pertussis, Pasteurella multocida*

Gram positive anaerobes; *Clostridium perfringens, Peptococcus niger, Propionibacterium acnes*
Gram negative anaerobes; *Bacteroides melaninogenicus*
Spirochete: *Borrelia burgdorferi, Treponema pallidum*
Campylobacter: *Campylobacter jejuni*

The principal metabolite of clarithromycin is a microbiologically active metabolite, 14-OH clarithromycin. This metabolite is as active or 1 to 2 fold less active than the parent compound for most organisms, except for *H. influenzae* against which it is twice as active. The parent compound and the 14-OH-metabolite exert either an additive or synergistic effect on *H. influenzae in vitro* and *in vivo*, depending on bacterial strains. In addition to this, 14-OH metabolite is 4-7 times less effective against *Mycobacterium avium* complex (MAC) isolates. Clinical significance of this activity is unknown against *Mycobacterium avium* complexes.

Susceptibility tests
Quantitative methods that require measurement of zone diameters give the most precise estimates of susceptibility of antibiotic. One recommended procedure uses discs impregnated with 15 µg of clarithromycin for testing susceptibility (Kirby-Bauer diffusion test); interpretations correlate inhibition zone diameters of this disc test with MIC values for clarithromycin. The MIC's are determined by the broth or agar dilution method.

With these procedures, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infective organism is not likely to respond to therapy. A report of "Intermediate Susceptibility" suggests the therapeutic effect of the medicine may be equivocal or that the organism would be susceptible if higher doses were used (intermediate susceptibility also referred to as moderately susceptible).

For absolute limits as to susceptible, resistant and intermediate susceptibility; please refer to country- or region-specific data.

5.2. Pharmacokinetic properties
General properties
Clarithromycin is an antibiotic with antimicrobial effect. It is slightly soluble in ethanol, methanol and acetonitrile and it is insoluble in water.

Absorption:
Clarithromycin is rapidly and well absorbed from the gastrointestinal tract (stomach-intestine). The absolute bioavailability of clarithromycin tablet is approximately 50%. Food intake immediately before dosing increases clarithromycin bioavailability by a mean of 25%. Overall, this increase is minor and should be of little clinical significance with the recommended dosing regimens. Therefore clarithromycin can be taken on an empty or full stomach.

With b.i.d. dosing at 500 mg, the steady state C_{max} for clarithromycin and its hydroxylated metabolite were achieved by the fifth dose. After the 5^{th} and 7^{th} doses, the steady state C_{max} for clarithromycin averaged 2.7 and 2.9 µg/ml; its hydroxylated metabolite averaged 0.88 and 0.83 µg/ml respectively. The half-life of the parent drug at the 500 mg dose level was 4.5 to 4.8 hours, while that of the 14-hydroxyclarithromycin was 6.9 to 8.7 hours. At steady state the 14-hydroxyelarithromycin levels did not increase proportionately with the clarithromycin dose, and the apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at the higher doses.

Distribution:
Clarithromycin and the 14-OH clarithromycin metabolite distribute readily into body tissues and fluids. Limited data from a small number of patients suggests clarithromycin does not achieve significant levels in cerebrospinal fluid after oral doses. Concentrations in tissues are usually several fold higher than serum concentrations. Examples from tissue and serum concentrations are presented below.

CONCENTRATION (after 250 mg q12 h)		
Tissue Type	**Tissue (µg/g)**	**Serum (µg/ml)**
Tonsil	1.6	0.8
Lung	8.8	1.7

Biotransformation:
With a dose 250 mg every 12 hours, the principal metabolite, 14-OH clarithromycin, attains a peak steady-state concentration of about 0.6 µg/ml and has an elimination half-life of 5 to 6 hours. With a dose 500 mg every 12 hours, the peak steady-state concentration of 14-OH clarithromycin is slightly higher (up to 1 µg/ml), and its elimination half-life is about 7 hours. With any of these dosing regimens, the steady-state concentration of this metabolite is generally attained within 2 to 3 days.

Elimination
In human adults given single oral doses of 250 mg or 1200 mg clarithromycin, urinary excretion accounted for 37.9% of the lower dose and 46.0% of the higher dose. Fecal elimination accounted for 40.2% and 29.1% (this included a subject with only one stool sample containing 14.1%) of these respective doses.

Linearity/Non-linearity
This non-linear pharmacokinetic behavior of clarithromycin, coupled with the overall decrease in the formation of 14-hydroxylation and N-demethylation products at the higher doses, indicates the non-linear metabolism of clarithromycin becomes more pronounced at high doses.

Characteristics in patients
Hepatic Impairment:
In a study comparing one group of healthy human subjects with a group of subjects with liver impairment who were given 250 mg of clarithromycin b.i.d. for two days and a single 250 mg dose the third day, steady state plasma levels and systemic clearing of clarithromycin were not significantly different between the two groups. In contrast, steady state concentrations of the 14-OH metabolite were markedly lower in the group of hepatic-impaired subjects. This decreased metabolic clearance of the parent compound by 14-hydroxylation was partially offset by an increase in the renal clearance of parent drug, resulting in comparable steady state levels of parent drug in the hepatic impaired and healthy subjects. These results indicate that no adjustment of dosage is necessary for subjects with moderate or severe hepatic impairment but with normal renal function.

Renal Impairment:
The plasma levels, half-life, C_{max} and C_{min} for both clarithromycin and its 14-OH metabolite were higher and AUC was larger in subjects with renal impairment. K_{elim} and urinary excretion were lower. The extent to which these parameters differed was correlated with the degree of renal impairment; the more severe the renal impairment, the more significant the difference (see section 4.2).

In Elderly:
In the elderly group, circulating plasma levels were higher and elimination slower than in the younger group for both parent drug and 14-OH metabolite. However, there was no difference between the two groups when renal clearance was correlated with creations clearance. It is concluded from those results that any effect on the handling of clarithromycin is related to renal function and not to age itself.

Mycobacterium avium Infections
Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of 500 mg doses of clarithromycin every 12 hours to adult patients with HIV infection were similar to those observed in normal subjects. However, at the higher doses which may be required to treat *Mycobacterium avium* infections, clarithromycin concentrations were much higher than those observed at the usual doses. In adult HIV-infected patients taking 1000 and 2000 mg/day in two divided doses, steady-state clarithromycin C_{max} values ranged from 2 to 4 µg/ml and 5 to 10 µg/ml, respectively. Elimination half-lives appeared to be lengthened at these higher doses as compared to those seen with usual doses in normal subjects. The higher plasma concentrations and longer elimination half-lives observed at these doses are consistent with the known nonlinearity in clarithromycin pharmacokinetics.

Concomitant Omeprazole Administration
The mean omeprazole AUC_{0-24}, was 89% greater and the harmonic mean for omeprazole $t_{1/2}$ was 34% greater when omeprazole was administered with clarithromycin than when omeprazole was administered alone. When clarithromycin was administered with omeprazole, the steady state C_{max}, C_{min} and AUC_{0-8} of clarithromycin were increased by 10%, 27%, and 15%, respectively, over values achieved when clarithromycin was administered with placebo.

At steady state, clarithromycin gastric mucous concentrations six hours post-dosing were approximately 25-fold higher in the clarithromycin/omeprazole group compared with the clarithromycin alone group.

6 hours post-dosing, mean clarithromycin gastric tissue concentrations were approximately 2-fold higher when clarithromycin was given with omeprazole than when clarithromycin was given with placebo.

5.3 Preclinical safety data

Acute, Subchronic, and Chronic Toxicity:
Studies were conducted in mice, rats, dogs and/or monkeys with clarithromycin administered orally. The duration of administration ranged from a single oral dose to repeated daily oral administration for 6 consecutive months. In acute mouse and rat studies, 1 rat, but no mice, died following a single gavage of 5 g/kg body weight. The median lethal dose, therefore, was greater than 5 g/kg, the highest feasible dose for administration.

No adverse effects were attributed to clarithromycin in primates exposed to 100 mg/kg/day for 14 consecutive days or to 35 mg/kg/day for 1 month. Similarly, no adverse effects were seen in rats exposed to 75 mg/kg/day for 1 month, to 35 mg/kg/day for 3 months, or to 8 mg/kg/day for 6 months. Dogs were more sensitive to clarithromycin, tolerating 50 mg/kg/day for 14 days, 10 mg/kg/day for 1 and 3 months, and 4 mg/kg/day for 6 months without adverse effects.

The major clinical signs at toxic doses in these studies described above included emesis, weakness, reduced food consumption and reduced weight gain, salivation, dehydration, and hyperactivity. 2 of 10 monkeys receiving 400 mg/kg/day died on treatment day 8; yellow discolored feces were passed on a few isolated occasions by some surviving monkeys given a dose of 400 mg/kg/day for 28 days.

The primary target organ at toxic dosages in all species was the liver. The development of hepatotoxicity in all species was detectable by early elevation of serum concentrations of alkaline phosphatase, alanine and aspartate aminotransferase, gamma-glutamyl transferase, and/or lactic dehydrogenase. Discontinuation of the drug generally resulted in a return to normal concentrations of these specific parameters.

Additional tissues less commonly affected in the various studies included the stomach, thymus and other lymphoid tissues, and the kidneys. Conjunctival injection and lacrimation, following near therapeutic dosages, occurred in dogs only. At a massive dosage of 400 mg/kg/day, some dogs and monkeys developed corneal opacities and/or edema.

Fertility, Reproduction, and Teratogenicity:
Fertility and reproduction studies have shown daily dosages of 150 to 160 mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, and number and viability of offspring.

Two teratogenicity studies in both Wistar (po) and Sprague-Dawley (po and IV) rats, one study in New Zealand White rabbits and one study in cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin. Only in one additional study in Sprague-Dawley rats at similar doses and essentially similar conditions did a very low, statistically insignificant incidence (approximately 6%) of cardiovascular anomalies occur. These anomalies appeared to be due to spontaneous expression of genetic changes within the colony. Two studies in mice also revealed a variable incidence of cleft pal at (3 to 30%) following doses of 70 times the upper range of the usual daily human clinical dose (500 mg b.i.d.), but not at 35 times the maximal daily human clinical dose, suggesting maternal and fetal toxicity but not teratogenicity.

Clarithromycin has been shown to produce embryonic loss in monkeys when administered at approximately 10 times the upper range of the usual daily human dose (500 mg b.i.d.), starting at gestation day 20. This effect has been attributed to maternal toxicity of the medicine at very high doses. An additional study in pregnant monkeys at dosages of approximately 2.5 to 5 times the maximal intended daily dosage produced no unique hazard to the fetus.

A dominant lethal test in mice given 1000 mg/kg/day (approximately 70 times the maximal human daily clinical dose) was clearly negative for any mutagenic activity, and, in a Segment I study of rats treated with up to 500 mg/kg/day (approximately 35 times the maximal daily human clinical dose) for 80 days, no evidence of functional impairment of male fertility due to this long-term exposure to these very high doses of clarithromycin was exhibited.

Mutagenicity:
Studies to evaluate the mutagenic potential of clarithromycin were performed using both nonactivated and rat-liver-microsome-activated test systems (Ames Test). Results of these studies provided no evidence of mutagenic potential at drug concentrations of 25 µg/Petri plate or less. At a concentration of 50 µg the medicine was toxic for all strains tested.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Microcrystalline cellulose
Polyvinylpyrrolidone
Colloidal silicon dioxide
Magnesium stearate
Talc
Film coating agent
Opadry 03B 22320 yellow (Indigo carmine, tartrazine, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
48 months

6.4 Special precautions for storage
Store at room temperature below 30°C and in a dry place.

6.5 Nature and contents of container
Blisters of 7 tablets coated with transparent PVDC on one side and printed aluminum foil on the other side. Each cardboard box contains 14 tablets.

6.6 Special precautions for disposal and other handling
Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER
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8. MARKETING AUTHORIZATION NUMBER

189/31

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10. DATE OF REVISION OF THE SPC

12.07.2018