

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Klaram 250 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg of clarithromycin

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, oval, biconvex marked with `250` on one side and 'CL' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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

Clarithromycin is indicated for the treatment of infections due to susceptible organisms. Such infections include:-

1. Lower respiratory tract infections (e.g. bronchitis, pneumonia).
2. Upper respiratory tract infections (e.g. pharyngitis, sinusitis).
3. Skin and soft tissue infections (e.g. folliculitis, cellulitis, erysipalis).
4. Disseminated or localised mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare*. Localised infections due to *Mycobacterium chelonae*, *Mycobacterium fortuitum* or *Mycobacterium kansasii*.
5. Clarithromycin is indicated for the prevention of disseminated *Mycobacterium avium* complex infection in HIV - infected patients with CD4 lymphocyte counts less than or equal to 100/mm³.
6. Clarithromycin in the presence of acid suppression is indicated for the eradication of *H. pylori*, resulting in decreased recurrence of duodenal ulcer. (See further information).

As with other antibiotics, it is recommended that guidelines on the prevalence of local resistance, and associated medical practice regarding the prescription of antibiotics, be consulted before prescribing clarithromycin.

Further Information: *H. pylori* is strongly associated with peptic ulcer disease. 90 to 100% of patients with duodenal ulcers are infected with this agent. Eradication of *H. pylori* has been shown to markedly reduce the rate of duodenal ulcer recurrence, thereby reducing the need for maintenance anti-secretory therapy. In a well-controlled double-blind study, *H. pylori* infected patients with duodenal ulcer received clarithromycin 500 mg TID for 14 days with omeprazole 40 mg daily for 28 days. Clarithromycin has been used in other treatment regimens for the eradication of *H. pylori*. These regimens include: Clarithromycin plus tinidazole and omeprazole; and clarithromycin plus tetracycline, bismuth subsalicylate, and ranitidine.

4.2 Posology and method of administration

Adults and children older than 12 years

The usual recommended dosage of clarithromycin in adults is one 250 mg tablet twice daily. In more severe infections, the dosage can be increased to 500 mg twice daily. The usual duration of therapy is 6 to 14 days.

Children younger than 12 years

Use of clarithromycin tablets is not recommended for children younger than 12 years. Use clarithromycin oral suspension.

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, 250 mg twice daily in more severe infections. Treatments should not be continued beyond 14 days in these patients.

Dosage in patients with mycobacterial infections: The recommended starting dose is 500 mg twice daily. If no clinical or bacteriologic response is observed in 3 to 4 weeks, the dose may be increased to 1000 mg twice daily. Treatment of disseminated *Mycobacterium Avium* Complex (MAC) infections in AIDS patients should be continued, as long as clinical microbiological benefit is demonstrated. Clarithromycin should be used in conjunction with other antimycobacterial agents.

Treatment of other non-tuberculous mycobacterial infections should continue at the discretion of the physician.

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

Eradication of H. pylori:

Dual Therapy (14 days)

The recommended dose of clarithromycin is 500 mg three times daily for 14 days. (See further information).

Triple Therapy (7 days)

Clarithromycin 500 mg twice daily and a proton pump inhibitor (at the approved daily dose)* should be given with amoxicillin 1000 mg twice daily for 7 days.

Triple Therapy (7 days)

Clarithromycin 500 mg twice daily and a proton pump inhibitor (at the approved daily dose)* should be given with metronidazole 400 mg twice daily for 7 days.

Triple Therapy (7-10 days)

Clarithromycin 500 mg twice daily should be given with amoxicillin 1000 mg twice daily and omeprazole 20 mg daily for 7 to 10 days.

*see individual data sheets/ SPCs for the dose recommended for *H.pylori* eradication.

4.3 Contraindications

Use in patients with known hypersensitivity to macrolide antibiotic drugs or any of its excipients.

Use in patients with severe impairment of hepatic function, in combination with renal impairment.

Clarithromycin and ergotamine or dihydroergotamine derivatives should not be co-administered, as this may result in ergot toxicity.

Concomitant administration of clarithromycin and any of the following drugs is contra-indicated: astemizole, cisapride, pimozone and terfenadine. Elevated cisapride, pimozone and terfenadine levels have been reported in patients receiving either of these drugs and clarithromycin concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular fibrillation and Torsade de Pointes (see section 4.5). Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including Torsades de Pointe (see section 4.4 and 4.5).

Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins), lovastatin or simvastatin, due to the risk of rhabdomyolysis. Treatment with these agents should be discontinued during clarithromycin treatment (see section 4.4).

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

4.4 Special warnings and precautions for use

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

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

Clarithromycin is excreted principally by the liver and kidney, therefore caution must be exercised in its use in patients with impaired hepatic or renal function or in those concomitantly receiving potentially hepatotoxic drugs.

Cases of fatal hepatic failure (see section 4.8) have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Prolonged or repeated use of clarithromycin may result in overgrowth of non-susceptible bacteria. If super-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see section 4.5). If concomitant administration of colchicine and clarithromycin is necessary, patients should be monitored for clinical symptoms of colchicine toxicity.

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 anti bacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*.

CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of anti bacterial 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.

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

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

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

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

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, and toxic epidermal necrolysis, 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).

HMG-CoA reductase inhibitors: Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3). As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (see section 4.5). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly. Patients should be monitored for signs and symptoms of myopathy. Rare reports of rhabdomyolysis have also been reported in patients taking atorvastatin or rosuvastatin concomitantly with clarithromycin. When used with clarithromycin, atorvastatin or rosuvastatin should be administered in the lowest possible doses. Adjustment of the statin dose or use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin or pravastatin) should be considered.

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 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 colonization with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

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

well as lincomycin and clindamycin.

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 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.

Ergotamine/dihydroergotamine

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).

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-(R)-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. 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. 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-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 be considered:

- For patients with CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%.
- For patients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%.
- Doses of clarithromycin greater than 1 gm/day should not be coadministered 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, Bi-directional drug interactions).

Effect of Clarithromycin on Other Medicinal Products

Antiarrhythmics

There have been postmarketing reports of Torsade de Pointes occurring with the 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 these medications should be monitored during clarithromycin therapy.

CYP3A4-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: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin), pimozone, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, 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}, AUC₀₋₂₄, 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 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.

Theophylline, carbamazepine

Results of clinical studies indicate that there was a modest but statistically significant ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels when either of these drugs were administered concomitantly with clarithromycin. Dose reduction may need to be considered.

Tolterodine

The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population

subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor 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 and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. 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 (see section 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. 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 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.

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.

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 bid) and saquinavir (soft gelatine capsules, 1200 mg tid) 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 coadministered 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 the combination therapy of saquinavir and ritonavir, therefore when this combination therapy is co-administered with clarithromycin consideration should be given to the potential effects of ritonavir on clarithromycin.

Verapamil

Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

4.6 Fertility, pregnancy and lactation

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

Clarithromycin is excreted into human breast 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

a. Summary of the safety profile

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. (see section b of section 4.8)

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

b. Tabulated summary of adverse reactions

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

The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) 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.

System Organ Class	Very common $\geq 1/10$	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1,000$ to $< 1/100$	Not Known (cannot be estimated from the available data)
Infections and infestations			Candidiasis, vaginal infection	Pseudomembranous colitis, erysipelas, erythrasma
Blood and lymphatic system			Leukopenia, neutropenia, eosinophilia	Agranulocytosis, thrombocytopenia
Immune system disorders ¹			Hypersensitivity	Anaphylactic reaction
Metabolism and nutrition disorders			Anorexia, decreased appetite	Hypoglycaemia ²
Psychiatric disorders		Insomnia	Anxiety	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams
Nervous system disorders		Dysgeusia, headache, taste perversion	Dizziness, somnolence ² , tremor	Convulsion, ageusia, parosmia, anosmia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Electrocardiogram QT prolonged ¹ , palpitations	Torsade de pointes ¹ , ventricular tachycardia ¹
Vascular disorders				Hemorrhage ²
Gastrointestinal disorders		Diarrhea ¹ , vomiting, dyspepsia, nausea, abdominal pain	Gastritis, stomatitis, glossitis, abdominal distension, constipation, dry mouth, eructation, flatulence	Pancreatitis acute, tongue discolouration, tooth discoloration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis, hepatitis, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased	Hepatic failure ¹ , jaundice hepatocellular
Skin and		Rash,	Pruritus, urticaria	Stevens-Johnson

subcutaneous tissue disorders		hyperhidrosis		syndrome ¹ , toxic epidermal necrolysis ¹ , drug rash with eosinophilia and systemic symptoms (DRESS), acne
Musculoskeletal and connective tissue disorders				Rhabdomyolysis ¹ , 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 normalised ratio increased ² , prothrombin time prolonged ² , urine color abnormal

¹ See section a)

² See section c)

c. Description of selected adverse reactions

In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications (see section 4.4).

A special attention to diarrhoea should be paid as *Clostridium difficile*-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhea to fatal colitis. (see section 4.4)

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome and toxic epidermal necrolysis, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated (see section 4.4).

As with other macrolides, QT prolongation, ventricular tachycardia, and *torsade de pointes* have rarely been reported with clarithromycin (see section 4.4 and 4.5).

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents (see section 4.4).

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 colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in elderly and/or patients with renal insufficiency, some with a fatal outcome. (see sections 4.4 and 4.5).

There have been rare reports of hypoglycemia, some of which have occurred in patients on concomitant oral hypoglycemic agents or insulin (see section 4.4 and 4.5).

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 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 (see section 4.4 and 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 diarrhea. 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)

d. 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 should use clarithromycin paediatric suspension. There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age.

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

e. Other special populations

Immunocompromised patients

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

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

In these immunocompromised patients, evaluations of laboratory values were made by 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 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.

4.9 Overdose

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and general supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

One patient who has a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.

The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or two-fold higher than the MICs of the parent compound, except for *H. influenzae* where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Klaram is usually active against the following organisms in vitro. Please see below for table of MIC breakpoints.

- Gram-positive Bacteria: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes* (Group A beta-hemolytic streptococci); alpha-hemolytic streptococci (viridans group); *Streptococcus* (Diplococcus) *pneumoniae*; *Streptococcus agalactiae*; *Listeria monocytogenes*.
- Gram-negative Bacteria: *Haemophilus influenzae*; *Haemophilus parainfluenzae*; *Moraxella* (Branhamella) *catarrhalis*; *Neisseria gonorrhoeae*; *Legionella pneumophila*; *Bordetella pertussis*; *Helicobacter pylori*; *Campylobacter jejuni*.
- Mycoplasma: *Mycoplasma pneumoniae*; *Ureaplasma urealyticum*.

Other Organisms: *Chlamydia trachomatis*; *Mycobacterium avium*; *Mycobacterium leprae*.

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

Clarithromycin has bactericidal activity against several bacterial strains. The organisms include *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Moraxella* (Branhamella) *catarrhalis*, *Neisseria gonorrhoeae*, *H. pylori* and *Campylobacter* spp.

H. pylori is associated with acid peptic disease including duodenal ulcer and gastric ulcer in which about 95% and 80% of patients respectively are infected with the agent. *H. pylori* is also implicated as a major contribution factor in the development of gastric and ulcer recurrence in such patients.

Clarithromycin has been used in small numbers of patients in other treatment regimens. Possible kinetic interactions have not been fully investigated. These regimens include:

- Clarithromycin plus tinidazole and omeprazole; clarithromycin plus tetracycline, bismuth subsalicylate and ranitidine; clarithromycin plus ranitidine alone.
- Clinical studies using various different *H. pylori* eradication regimens have shown that eradication of *H. pylori* prevents ulcer recurrence.

Breakpoints

The following breakpoints for clarithromycin, separating susceptible organisms from resistant organisms, have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST).

Breakpoints (MIC, µg/ml)		
Microorganism	Susceptible (≤)	Resistant (>)
<i>Streptococcus</i> spp.	0.25 µg/ml	0.5 µg/ml
<i>Staphylococcus</i> spp.	1 µg/ml	2 µg/ml
<i>Haemophilus</i> spp.	1 µg/ml	32 µg/ml
<i>Moraxella catarrhalis</i>	0.25 µg/ml	0.5 µg/ml

Clarithromycin is used for the eradication of *H. pylori* ; minimum inhibitory concentration (MIC) ≤ 0.25 µg/ml which has been established as the susceptible breakpoint by the Clinical and Laboratory Standards Institute (CLSI).

5.2 Pharmacokinetic properties

Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of Klaram tablets. The microbiologically active metabolite 14-hydroxyclearithromycin is formed by first pass metabolism. Klaram may be given without regard to meals as food does not affect the extent of bioavailability of Klaram tablets. Food does slightly delay the onset of absorption of clarithromycin and formation of the 14-hydroxymetabolite. The pharmacokinetics of clarithromycin are non linear; however, steady-state is attained within 2 days of dosing. At 250 mg b.i.d. 15-20% of unchanged drug is excreted in the urine. With 500 mg b.i.d. daily dosing urinary excretion is greater (approximately 36%). The 14-hydroxyclearithromycin is the major urinary metabolite and accounts for 10-15% of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5-10% of the parent drug is recovered from the faeces.

When clarithromycin 500 mg is given three times daily, the clarithromycin plasma concentrations are increased with respect to the 500 mg twice daily dosage.

Klaram provides tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Clarithromycin is 80% bound to plasma proteins at therapeutic levels. Klaram also penetrates the gastric mucus. Levels of clarithromycin in gastric mucus and gastric tissue are higher when clarithromycin is co-administered with omeprazole than when clarithromycin is administered alone.

5.3 Preclinical safety data

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

In repeated dose studies, toxicity was related to dose, duration of treatment and species. Dogs were more sensitive than primates or rats. The major clinical signs at toxic doses included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity.

In all species the liver was the primary target organ at toxic doses. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected included the stomach, thymus and other lymphoid tissues and the kidneys. At near therapeutic doses, conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.

Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomolgous monkeys failed to demonstrate any teratogenicity from clarithromycin. However, a further similar study in Sprague-Dawley rats indicated a low (6%) incidence of cardiovascular abnormalities which appeared to be due to spontaneous expression of genetic changes. Two mouse studies revealed a variable incidence (3-30%) of cleft palate and embryonic loss was seen in monkeys but only at dose levels which were clearly toxic to the mothers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
 Starch, pregelatinised
 Croscarmellose sodium
 Povidone (k-value 81.0 – 96.3)
 Talc
 Magnesium stearate
 Silica, colloidal anhydrous
 Opadry II, 40L22445 Yellow containing:
 Titanium dioxide (E171)
 Polydextrose (E1200)

Hypromellose (E464)
Triacetin (E1518)
Macrogol
Quinoline yellow (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Al/PVC/PVdC Strip or HDPE Tablet Container with LDPE Cap
Pack sizes: 7, 14, 21, 28, 30, 50, 100, 250, 500 or 1000 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland

8 MARKETING AUTHORISATION NUMBER

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