

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Clarithromycine ratiopharm 250 mg, filmomhulde tabletten
Clarithromycine ratiopharm 500 mg, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

{Product name} 250 mg

Each film-coated tablet contains 250 mg clarithromycin.

{Product name} 500 mg

Each film-coated tablet contains 500 mg clarithromycin.

Excipients with known effect:

{Product name} 250 mg contains 0.30 mg tartrazine aluminium lake (E102) and 0.008 mg allura red aluminium lake (E129).

{Product name} 500 mg contains 0.14 mg tartrazine aluminium lake (E102) and 0.001 mg allura red aluminium lake (E129).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

{Product name} 250 mg

Yellow, film-coated oval shaped tablet, debossed with “93” on one side and “7157” on the other.

Length: 17 mm Width: 8 mm Thickness: 5-6 mm

{Product name} 500 mg

Light yellow, film-coated oval shaped tablet, debossed with “93” on one side and “7158” on the other.

Length: 22 mm Width: 11 mm Thickness: 6.7-7.7 mm

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

{Product name} is indicated in adults and adolescents 12 years and older for the treatment of the following infections, when caused by clarithromycin-susceptible bacteria (see sections 4.4 and 5.1):

- Bacterial pharyngitis
- Acute bacterial sinusitis
- Acute bacterial exacerbation of chronic bronchitis
- Mild to moderate community acquired pneumonia
- Skin infections and soft tissue infections of mild to moderate severity, for example folliculitis, cellulites and erysipelas.

{Product name} can also be used in appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing agent for the eradication of *H. pylori* in patients with *H. pylori* associated ulcers (see section 4.2).

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

4.2 Posology and method of administration

The dosage of {Product name} depends on the clinical condition of the patient and has to be defined in any case by the physician.

250 and 500 mg tablets are available.

Posology

Adults and adolescents (12 years and older)

The recommended dose is 250 mg twice daily.

In severe infections, the dose may be increased to 500 mg twice daily.

Paediatric population (younger than 12 years)

{Product name} tablets are not suitable for children under 12 years of age weighing less than 30 kg. Other pharmaceutical forms (e.g. suspensions) are more adapted for these patients. Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age.

For children with weight more than 30 kg, dosage for adults and adolescents is applicable.

Elderly people (65 years or older)

As for adults.

Eradication of *H. pylori* in adults

In patients with gastro-duodenal ulcers due to *H. pylori* infection clarithromycin can be used in a dose of 500 mg twice daily during the eradication therapy in combination with amoxicillin 1000 mg twice daily and omeprazole 20 mg twice daily.”

Renal impairment

In patients with renal impairment with creatinine clearance less than 30 mL/min, the dosage of clarithromycin should be reduced by one half, e.g. 250 mg once daily or 250 mg twice daily in more severe infections. Treatment should not be continued beyond 14 days in these patients.

Hepatic impairment

Caution should be exercised when administering clarithromycin in patients with hepatic impairment (see sections 4.3 and 4.4).

Duration of therapy

The duration of therapy with clarithromycin depends on the clinical condition of the patient and in any case shall be determined by the physician.

- The usual duration of treatment is 6 to 14 days.
- Therapy should be continued at least for 2 days after symptoms have subsided.
- In β -haemolytic streptococcal infections the duration of therapy should be at least 10 days in order to prevent complications such as rheumatic fever and glomerulonephritis.
- Combination therapy for the eradication of *H. pylori* infection, e.g. clarithromycin 500 mg (two 250 mg tablets or one 500 mg tablet) twice daily in combination with amoxicillin 1000 mg twice daily and omeprazole 20 mg twice daily should be continued for 7 days.

Method of administration

{Product name} may be given without regard to food intake (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance, to other macrolide antibiotic drugs or to any of the excipients listed in section 6.1.

- Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, domperidone, pimoziide or terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see sections 4.4 and 4.5).
- Concomitant administration with ticagrelor, ivabradine or ranolazine is contraindicated.
- Concomitant administration of clarithromycin and ergot alkaloids (e.g. ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity (see section 4.5).
- Concomitant administration of clarithromycin and lomitapide is contraindicated (see section 4.5).
- Concomitant administration of clarithromycin and oral midazolam is contraindicated (see section 4.5).
- Clarithromycin must not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (see sections 4.4 and 4.5).
- Clarithromycin must not be used concomitantly with HMG-CoA reductase inhibitors (statins), that are extensively metabolised by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy including rhabdomyolysis (see sections 4.4 and 4.5).
- As with other strong CYP3A4 inhibitors, clarithromycin must not be used in patients taking colchicine (see sections 4.4 and 4.5).
- Clarithromycin must not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of the QT interval).
- Clarithromycin is contraindicated in patients who suffer from severe hepatic failure in combination with renal impairment.

4.4 Special warnings and precautions for use

Pregnancy

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

Hepatic impairment

Clarithromycin is principally metabolised by the liver. Therefore, caution should be exercised in administering the 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.

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.

Renal impairment

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

Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.

Diarrhoea and colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, and may range in severity from mild to life-threatening. *Clostridium difficile*- associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*. 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 antibacterial agents. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

Colchicine

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in elderly and/or patients with renal insufficiency, some with a fatal outcome (see sections 4.5 and 4.8). Concomitant administration of clarithromycin and colchicine is contraindicated (see section 4.3).

Triazolobenzodiazepines

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

Aminoglycosides

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.

Cardiovascular events

Prolongation of the QT interval, reflecting effects on cardiac repolarisation, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in patients treated with macrolides including clarithromycin (see section 4.8).

Due to increased risk of QT prolongation and ventricular arrhythmias (including torsade de pointes), the use of clarithromycin is contraindicated

- in patients taking any of astemizole, cisapride, domperidone, pimozone and terfenadine;
- in patients with electrolyte disturbances such as hypomagnesaemia or hypokalaemia;
- and in patients with a history of QT prolongation or ventricular cardiac arrhythmia (see section 4.3).

Furthermore, clarithromycin should be used with caution in the following patients:

- Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia;
- Patients concomitantly taking other medicinal products associated with QT prolongation other than those which are contraindicated (see section 4.5).

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

Pneumonia

In view of the emerging resistance of *Streptococcus 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*, acne vulgaris, and erysipelas and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g. Acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms (DRESS)), clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

HMG-CoA reductase inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3). Caution should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathy. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered (see section 4.5).

Oral hypoglycaemic agents/insulin

The concomitant use of clarithromycin and oral hypoglycaemic agents (such as sulphonylureas) and/or insulin can result in significant hypoglycaemia. Careful monitoring of glucose is recommended (see section 4.5).

Oral anticoagulants

There is a risk of serious haemorrhage and significant elevations in International Normalised 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.

Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban, apixaban and edoxaban, particularly to patients at high risk of bleeding (see section 4.5).

Helicobacter pylori

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

Superinfections

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

Cross resistance

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

CYP3A4-interactions

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

Excipients

Tartrazine aluminium lake and allura red aluminium lake

This medicinal product contains tartrazine aluminium lake (E102) and allura red aluminium lake (E129) which may cause allergic reactions.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Astemizole, cisapride, domperidone, pimozone 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 pimozone concomitantly (see section 4.3).

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias, such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes (see section 4.3). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in 2- to 3-fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Concomitant use of clarithromycin and colchicine is contraindicated (see sections 4.3 and 4.4).

Ergot alkaloids

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

HMG-CoA reductase inhibitors (statins)

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

Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered. Patients should be monitored for signs and symptoms of myopathy.

Lomitapide

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

Oral midazolam

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 7-fold after oral administration of midazolam. Concomitant administration of oral midazolam and clarithromycin is contraindicated (see section 4.3).

Ticagrelor or ranolazine

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 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-OH-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Etravirine

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

Fluconazole

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

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. 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 creatinine clearance 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%.

For patients with creatinine clearance <30 mL/min the dose of clarithromycin should be decreased by 75%.

Doses of clarithromycin greater than 1000 mg/day should not be co-administered with ritonavir.

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

Effect of clarithromycin on other medicinal products

CYP3A-based interactions

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

The use of clarithromycin is contraindicated in patients receiving the CYP3A substrates astemizole, cisapride, domperidone, pimozone and terfenadine due to the risk of QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see sections 4.3 and 4.4).

The use of clarithromycin is also contraindicated with ergot alkaloids, oral midazolam, HMG CoA reductase inhibitors metabolised mainly by CYP3A4 (e.g. lovastatin and simvastatin), colchicine, ticagrelor, ivabradine and ranolazine (see section 4.3). Concomitant administration of clarithromycin with lomitapide is contraindicated due to the potential for markedly increased transaminases (see section 4.3).

Caution is required if clarithromycin is co-administered with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolised by this enzyme.

Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolised by CYP3A should be monitored closely in patients concurrently receiving clarithromycin. Drugs or drug classes that are known or suspected to be metabolised by the same CYP3A isozyme include (but this list is not comprehensive) alprazolam, carbamazepine, cilostazole, ciclosporin, disopyramide, ibrutinib, methylprednisolone, midazolam (intravenous), omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), quinidine, rifabutin, sildenafil, sirolimus, tacrolimus, triazolam and vinblastine. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Oral anticoagulants

Direct acting oral anticoagulants (DOACs)

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

Warfarin and acenocoumarol

In isolated cases, patients receiving combination therapy with clarithromycin and oral anticoagulants may experience increased pharmacologic effects and even toxic effects of these drugs. International normalized ratio (INR) or Prothrombin times should be carefully monitored while patients are simultaneously receiving clarithromycin and oral anticoagulants.

Antiarrhythmics

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

There have been post-marketing reports of hypoglycaemia with the concomitant administration of clarithromycin and disopyramide. Therefore, blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

Oral hypoglycaemic agents/insulin

With certain hypoglycaemic drugs such as nateglinide and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia when used concomitantly. Careful monitoring of glucose is recommended.

Omeprazole

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

Sildenafil, tadalafil and vardenafil

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

Theophylline and 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 metaboliser population.

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

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam. 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 metabolised by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not metabolised by CYP3A (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.

Aprepitant, eletriptan, halofantrine, and ziprasidone

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.

Corticosteroids

Caution should be exercised in concomitant use of clarithromycin with systemic and inhaled corticosteroids that are primarily metabolised by CYP3A due to the potential for increased systemic exposure to corticosteroids. If concomitant use occurs, patients should be closely monitored for systemic corticosteroid undesirable effects.

Other drug interactions

Aminoglycosides

Caution is advised regarding concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides (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 to allow for a 4-hour interval between each

medication. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolised by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.

Hydroxychloroquine and chloroquine

Clarithromycin should be used with caution in patients receiving these medicines known to prolong the QT interval due to the potential to induce cardiac arrhythmia and serious adverse cardiovascular events.

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 metabolised 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 bi-directional drug interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in *steady-state* AUC and C_{max} values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are co-administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see section 4.5).

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embryofetal development cannot be excluded. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results.

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

Breast-feeding

The safety of clarithromycin for use during breast feeding of infants has not been established. Clarithromycin is excreted into human breast milk in small amounts. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin.

Fertility

There is no data available on the effect of clarithromycin on fertility in humans. In the rat, fertility studies have not shown any evidence of harmful effects.

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 paediatric population are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics (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 pre-existing 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; frequency 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			Cellulitis ¹ , candidiasis,	Pseudomembranous colitis, erysipelas

			gastroenteritis ² , infection ³ , vaginal infection	
Blood and lymphatic system			Leukopenia, neutropenia ⁴ , thrombocythaemia ³ , eosinophilia ⁴	Agranulocytosis, thrombocytopenia
Immune system disorders			Anaphylactoid reaction ¹ , hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety, nervousness ³	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache	Loss of consciousness ¹ , dyskinesia ¹ , dizziness, somnolence ⁶ , tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest ¹ , atrial fibrillation ¹ , electrocardiogram QT prolonged, extrasystoles ¹ , palpitations	Torsade de pointes, ventricular tachycardia, ventricular fibrillation
Vascular disorders		Vasodilation ¹		Haemorrhage
Respiratory, thoracic and mediastinal disorder			Asthma ¹ , epistaxis ² , pulmonary embolism ¹	
Gastrointestinal disorders		Diarrhoea ⁵ , vomiting ⁵ , dyspepsia, nausea ⁵ , abdominal pain ⁵	Oesophagitis ¹ , gastrooesophageal reflux disease ² , gastritis, proctalgia ² , stomatitis, glossitis, abdominal distension ⁴ , constipation, dry mouth, eructation, flatulence	Pancreatitis acute, tongue discoloration, tooth discoloration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis ⁴ , hepatitis ⁴ , alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased ⁴	Hepatic failure, jaundice hepatocellular

Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous ¹ , pruritus, urticaria, rash maculo-papular ³	Severe cutaneous adverse reactions (SCAR) (e.g. acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS)), acne
Musculoskeletal and connective tissue disorders			Muscle spasms ³ , musculoskeletal stiffness ¹ , myalgia ²	Rhabdomyolysis ^{2,6} , myopathy
Renal and urinary disorders			Blood creatinine increased ¹ , blood urea increased ¹	Renal failure, nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis ^{1,6}	Injection site pain ^{1,6} , injection site inflammation ^{1,6}	Malaise ⁴ , pyrexia ³ , asthenia, chest pain ⁴ , chills ⁴ , fatigue ⁴	
Investigations			Albumin globulin ratio abnormal ¹ , blood alkaline phosphatase increased ⁴ , blood lactate dehydrogenase increased ⁴	International normalised ratio increased, 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.

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

² ADRs reported only for the Extended-Release Tablets formulation

³ ADRs reported only for the Granules for Oral Suspension formulation

⁴ ADRs reported only for the Immediate-Release Tablets formulation

⁵ See section a)

⁶ See section c)

c. Description of selected adverse reactions

Injection site phlebitis, injection site pain, vessel puncture site pain, and injection site inflammation are specific to the clarithromycin intravenous formulation.

In some reports of rhabdomyolysis, clarithromycin was administered concomitantly with other drugs known to be associated with rhabdomyolysis (such as statins, fibrates, colchicine or allopurinol) (see section 4.3 and 4.4).

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

There have been rare reports of clarithromycin extended-release tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal

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

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

d. Paediatric population

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. 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, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvate Transaminase (SGPT) elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 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.

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 listed in [Appendix V](#).

4.9 Overdose

Symptoms

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 behaviour, hypokalaemia and hypoxaemia.

Management

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 haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use, macrolide

ATC code: J01F A09

Mechanism of action

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.

PK/PD Relationship

Clarithromycin is extensively distributed in body tissues and fluids. Because of high tissue penetration, intracellular concentrations are higher than serum concentrations.

The most important pharmacodynamic parameters for predicting macrolide activity are not conclusively established. The time above MIC (T/MIC) may correlate best with efficacy for clarithromycin, however since clarithromycin concentrations achieved in respiratory tissues and epithelial lining fluids exceed those in plasma, using parameters based on plasma concentrations may fail to predict accurately the response for respiratory tract infections.

Mechanisms of resistance

Resistance mechanisms against macrolide antibiotics include alteration of the target site of the antibiotic or are based on modification and/or the active efflux of the antibiotic. Resistance development can be mediated via chromosomes or plasmids, be induced or exist constitutively. Macrolide-resistant bacteria generate enzymes which lead to methylation of residual adenine at ribosomal RNA and consequently to inhibition of the antibiotic binding to the ribosome. Macrolide-resistant organisms are generally cross-resistant to lincosamides and streptogramin B based on methylation of the ribosomal binding site. Clarithromycin ranks among the strong inducers of this enzyme as well. Furthermore, macrolides have a bacteriostatic action by inhibiting the peptidyl transferase of ribosomes.

A complete cross-resistance exists among clarithromycin, erythromycin and azithromycin. Methicillin-resistant staphylococci and penicillin-resistant *Streptococcus pneumoniae* are resistant to macrolides such as clarithromycin.

Breakpoints

The following breakpoints for clarithromycin, separating susceptible organisms from resistant organisms, have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST) 2010-04-27 (v 1.1)

Species-related breakpoints for clarithromycin ^{B,C}		
Pathogens	Susceptible ≤ (mg/L)	Resistant > (mg/L)
<i>Enterobacteriaceae</i>	-	-
<i>Pseudomonas</i> spp.	-	-
<i>Acinetobacter</i> spp.	-	-
<i>Staphylococcus</i> spp.	1	2
<i>Enterococcus</i> spp.	-	-
<i>Streptococcus</i> groups A, B, C, G	0,25	0.5
<i>Streptococcus pneumoniae</i> D	0.25	0.5
<i>Other streptococci</i>	IE	IE
<i>Haemophilus influenzae</i>	1	32
<i>Moraxella catarrhalis</i>	0.25	0.5

<i>Neisseria gonorrhoeae</i>	-	-
<i>Neisseria meningitidis</i>	-	-
Gram-positive anaerobes (except <i>Clostridium difficile</i>)	-	-
Gram-negative anaerobes	-	-
Non-species related break-points A	IE	IE

A. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table or footnotes. However, pharmacodynamic data for calculation of macrolide, lincosamines and streptogramins non-species related breakpoints are not robust, hence IE.

B. Erythromycin can be used to determine the susceptibility of the listed bacteria to the other macrolides (azithromycin, clarithromycin and roxithromycin).

C. Clarithromycin is used for the eradication of *H. pylori* (MIC \leq 0.25 mg/L for wild type isolates).

D. The correlation between *H. influenzae* macrolide MICs and clinical outcome is weak. Therefore, breakpoints for macrolides and related antibiotics were set to categorise wild type *H. influenzae* as intermediate.

IE – Insufficient evidence that the species in question is a good target for therapy with the drug.

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

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive microorganisms
<i>Corynebacterium diphtheriae</i>
<i>Streptococcus</i> Group F
Aerobic Gram-negative microorganisms
<i>Bordetella pertussis</i>
<i>Legionella</i> spp.
<i>Moraxella catarrhalis</i>
<i>Pasteurella multocida</i>
Anaerobes
<i>Clostridium</i> spp. other than <i>C. difficile</i>
Other microorganisms
<i>Chlamydia trachomatis</i>
<i>Chlamydia pneumoniae</i>
<i>Clamydophila psittaci</i>
<i>Mycoplasma pneumoniae</i>
<i>Mycobacterium</i> spp.
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
<i>Enterococcus</i> spp.+
<i>Staphylococcus aureus</i> (methicillin-susceptible and methicillin-resistant+)
<i>Staphylococcus epidermidis</i> +
<i>Streptococcus</i> Group A*, B, C, G
<i>Streptococcus viridans</i>
<i>Streptococcus pneumoniae</i> *+
Aerobic Gram-negative microorganisms
<i>Haemophilus influenzae</i> §

Helicobacter pylori
Anaerobes
Bacteroides spp.
Peptococcus / Peptostreptococcus spp.
Inherently resistant organisms
Aerobic Gram-negative microorganisms
Acinetobacter
Enterobacteriaceae
Pseudomonas aeruginosa
Anaerobes
Fusobacterium spp.
Other microorganisms
Mycobacterium tuberculosis

\geq 10% resistance in at least one country of the European Union

* Species against efficacy has been demonstrated in clinical investigations (if susceptible)

+ Indicates species for which a high rate of resistance (i.e. greater than 50%) have been observed in one or more area/country/region(s) of the EU

§ Breakpoints for macrolides and related antibiotics were set to categorise wild type *H. influenzae* as intermediate

Other information

Susceptibility and resistance of *Streptococcus pneumoniae* and *Streptococcus* spp. to clarithromycin can be predicted by testing erythromycin.

Most available clinical experience from controlled randomised clinical trials indicate that clarithromycin 500 mg twice daily in combination with another antibiotic e.g. amoxicillin or metronidazole and e.g. omeprazole (given at approved levels) for 7 days achieve $>$ 80% *H. pylori* eradication rate in patients with gastroduodenal ulcers. As expected, significantly lower eradication rates were observed in patients with baseline metronidazole-resistant *H. pylori* isolates. Hence, local information on the prevalence of resistance and local therapeutic guidelines should be taken into account in the choice of an appropriate combination regimen for *H. pylori* eradication therapy. Furthermore, in patients with persistent infection, potential development of secondary resistance (in patients with primary susceptible strains) to an antimicrobial agent should be taken into the considerations for a new treatment regimen.

5.2 Pharmacokinetic properties

Absorption

Clarithromycin is rapidly and well absorbed from the gastrointestinal tract - primarily in the jejunum - but undergoes extensive first-pass metabolism after oral administration. The absolute bioavailability of a 250 mg clarithromycin tablet is approximately 50%. Food slightly delays the absorption but does not affect the extent of bioavailability. Therefore, clarithromycin tablets may be given without regard to food. Due to its chemical structure (6-O-methylerythromycin) clarithromycin is quite resistant to degradation by stomach acid. Peak plasma levels of 1-2 $\mu\text{g/mL}$ clarithromycin were observed in adults after oral administration of 250 mg twice daily. After administration of 500 mg clarithromycin twice daily the peak plasma level was 2.8 $\mu\text{g/mL}$.

After administration of 250 mg clarithromycin twice daily the microbiologically active 14-hydroxy metabolite attains peak plasma concentrations of 0.6 $\mu\text{g/mL}$. *Steady-state* is attained within 2 days of dosing.

Distribution

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

Clarithromycin is approximately 80% bound to plasma proteins at therapeutic levels.

Biotransformation and elimination

Clarithromycin is rapidly and extensively metabolised in the liver involving the P450 cytochrome system. Metabolism involves mainly N-dealkylation, oxidation and stereospecific hydroxylation at position C 14.

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

After oral administration of radioactive clarithromycin 70-80% of the radioactivity was found in the faeces. Approximately 20-30% of clarithromycin is collected as the unchanged active substance in the urine. This proportion is increased when the dose is increased. Renal insufficiency increases clarithromycin levels in plasma, if the dose is not decreased.

Total plasma clearance has been estimated to approximately 700 ml/min, with a renal clearance of approximately 170 mL/min.

Special population

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

5.3 Preclinical safety data

In 4-week-studies in animals, toxicity of clarithromycin was found to be related to the dose and to the duration of the treatment. In all species, the first signs of toxicity were observed in the liver, in which lesions were seen within 14 days in dogs and monkeys. The systemic levels of exposure, related to this toxicity, are not known in detail, but toxic doses (300 mg/kg/day) were clearly higher than the therapeutic doses recommended for humans. Other tissues affected included the stomach, thymus and other lymphoid tissues as well as the kidneys. At near therapeutic doses conjunctival injection and lacrimation occurred only in dogs. At a dose of 400 mg/kg/day some dogs and monkeys developed corneal opacities and/or oedema. *In vitro* and *in vivo* studies showed that clarithromycin did not have genotoxic potential.

No mutagenic effects were found in *in vitro*- and *in vivo* -studies with clarithromycin. Studies on reproduction toxicity showed that administration of clarithromycin at doses 2x the clinical dose in rabbit (iv) and 10x the clinical dose in monkey (po) resulted in an increased incidence of spontaneous abortions. These doses were related to maternal toxicity. No embryotoxicity or teratogenicity was generally noted in rat studies. However, cardiovascular malformations were observed in two studies in rats treated with doses of 150 mg/kg/d.

In mice at doses 70x the clinical dose, cleft palate occurred at varying incidence (3-30%).

Clarithromycin has been found in the milk of lactating animals.

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

Clarithromycin has not been tested for carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Sodium starch glycolate (Type A)
Microcrystalline cellulose (E460)
Povidone (PVP K-30) (E1201)
Magnesium hydroxide (E528)
Croscarmellose sodium
Colloidal anhydrous silica
Stearic acid (E570)
Magnesium stearate (E470b)

Film-coating:

Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400
Tartrazine lake (E102)
Allura Red AC lake (E129)
Indigo carmine lake (E132)
Vanillin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

{Product name} 250 mg

Available in blister packs of transparent or white opaque PVC or PVC/PVdC lidded with aluminium foil of 8, 10, 12, 14, 14 calendar pack, 16, 20, 30, 100 & 120 (10x12) as hospital pack.

{Product name} 500 mg

Available in blister packs of transparent or white opaque PVC or PVC/PVdC lidded with aluminium foil for 8, 10, 14, 14 calendar pack, 16, 20, 21, 30, 42 and 100.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Ratiopharm GmbH
Graf-Arco-Str. 3
89079 Ulm
Duitsland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 111801, filmomhulde tabletten 250 mg
RVG 111802, filmomhulde tabletten 500 mg

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 11 februari 2014
Datum van laatste verlenging: 1 december 2015

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft de rubrieken 4.3, 4.4 en 4.5: 4 maart 2024.