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Clarithromycin

Clarithro-Natrapharm 125 mg/5 mL Granules for Oral Suspension



ANTIBACTERIAL (MACROLIDE)

PHARMACEUTICAL FORM Granules for Oral Suspension

Clarithromycin 50 mg/mL granules for oral suspension is indicated in adults, adolescents and children, 6 months to 12 years, for the treatment of the following acute and chronic bacterial infections, when caused by

- Infections of the upper respiratory tract such as tonsillitis/pharyngitis, as an alternative when beta lactam antibiotics are not appropriate.
 Acute offitis media in children.
 Infections of the lower respiratory tract such as community acquired pneumonia.
 Sinusitis and acute exacerbation of chronic bronchitis in adults and adolescents over 12 years of age.
- · Skin infections and soft tissue infections of mild to moderate severity.

In appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing medicinal product for the eradication of *Helicobacter pylori* in adult patients with *H. pylori* associated ulcers (see Dosage and method of administration).

The dose of clarithromycin depends on the clinical condition of the patient and has to be defined in any case by the

Adults and adolescents
Standard dose: The usual dose is 250 mg twice daily.
High dose treatment (severe infections): The usual dose may be increased to 500 mg twice daily in severe infections.

Elimination of Helicobacter pylori in adults
In patients with gastro-duodenal ulcers due to H. pylori infection clarithromycin as part of the first line triple therapy is given in a dose of 500 mg twice daily. The national recommendations for Helicobacter pylori eradication have to be considered.

num recommended doses should be reduced proportionately to renal impairment.

For 125 mg/5 mL oral suspension

Dose in renal functional impairment

Weight

Dose 2.5 mL twice daily 5 mL twice daily 7.5 mL twice daily 10 mL twice daily

Children weighing less than 8 kg should be treated based on their bodyweight

There is limited experience of treatment of children below 6 months of age.

For the indication community acquired pneumonia effect in children under 3 years of age is not documented.

Duration of therapy
The duration of therapy with clarithromycin depends on the clinical condition of the patient. The duration of therapy has

- The usual duration of treatment of children up to 12 years of age is 5 to 10 days.
 The usual duration of treatment of adults and adolescents is 6 to 14 days.
 Therapy should be continued at least for 2 days after symptoms have subsided.
 In Streptococcus pyogenes (as a beta-haemolytic streptococcal) infections the duration of therapy should be at least 10 days.
 Combination therapy for the eradication of H. pylori infection, e.g. clarithromycin 500 mg twice daily in combination with amoxicillin 1000 mg twice daily and omeprazole 20 mg twice daily should be continued for 7 days.

Before administration the granules must be reconstituted with water, see Direction for reconstitution. For administration after reconstitution an oral PE/PP-measuring syringe or a PP-measuring spoon are used.

Direction for reconstitution 125 mg/5 mL: Fill the bottle with 29.5mL of cold drinking water and shake well before every use.

eating or drinking something immediately after the intake of the suspension Clarithromycin may be given irrespective of food intake. Food does not affect the extent of bioavailability. Food does only slightly delay the onset of absorption of clarithromycin.

lypersensitivity to macrolide antibiotics or to any of its excipients.

Concomitant administration of clarithromycin and any of the following active substances is contraindicated: astemizole, cisapride, domperidone, pimozide, tefenadine as this may result in GT prolongation and cardiac arrhythmias, including ventricular tackpardia, ventruclar fibrillation, and Torsades de pointes (see Interaction with other medicinal products and other forms of interaction).

Concomitant administration of clarithromycin and ergot alkaloids (e.g. ergotamine or dihydroergotamine) contraindicated, as this may result in ergot toxicity (see Interaction with other medicinal products and other forms

Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsade de pointes (see Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction).

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

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

As with other strong CYP3A4 inhibitors, clarithromycin should not be used in patients taking colchicine (see Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction). Concomitant administration of clarithromycin and oral midazolam is contraindicated (see Interaction with other r

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 Pregnancy and lactation).

Caution is advised in patients with severe renal insufficiency (see Dosage and method of administration).

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis jaundice, has been reported with clarithromycin. This hepatic dystunction may be severe and is usually reversible. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

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 inseventy from milo tille-infeatening, closiflouin dillicia-associated diarnose (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in sevently from mild diarnose to fatal collitis. Treatment with antibacterial agents afters the normal flora of the colon, which may lead to overgrowth of C. difficile. CDAD must be considered in all patients who present with diarnose aflolwing antibiotic use, Careful circla 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 (incrobial testing should be performed and adequate treatment initiated. Medicinal products inhibiting peristalsis should be avoided.

. 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 Interaction with other medicinal products and other forms of interaction).

Concomitant administration of clarithromycin and colchicine is contraindicated (see Contra

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in treatment with macrolides including clarithromycin (see Undesirable effects). Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes), clarithromycin should be used with caution in the following patients;

- bradycardia

 Patients with electrolyte disturbances such as hypomagnesaemia. Clarithromycin must not be given to patients with hypokalaemia (see Contraindications).

 Patients concomitantly taking other medicinal products associated with QT prolongation (see Interaction with other medicinal products and other forms of interaction).

 Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfenadine is contraindications.
- ed (see Contraindications).

 Clarithromycin must not be
- ed (see Contramidications).

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

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.

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 medicinal product 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

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 essinophilia and systemic symptoms (DRESS), clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see Interaction with other medicinal products and other forms of interacti

HMG-CoA Reductase Inhibitors (statins use of clarithromycin with lovastatin or simvastatin is contraindicated (see Contraindications).

should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis has been reported in taking clarithromycin and statins. 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 Interaction with other medicinal products and other forms of interaction).

Careful monitoring of glucose is recommended (see Interaction with other medicinal products and other forms of

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 Interaction with other medicinal products and other forms of interaction). 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

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.

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

Interaction with other medicinal products and other forms of interaction
The use of the following medicinal products is strictly contraindicated due to the potential for severe medicinal
product interaction effects
Astemizole, cisapride, domperidone, pimozide and terfenadine.
Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may
result in CT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsade de
pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly (see
Contraindications).

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 CT prolongation, ventricular tachycardia, ventricular fibrillation and torsade de pointes (see Contraindications). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a two to three fold increase in the serum level of the acid-metabolite of terfenadine and in prolongation of the CT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Postmarketing 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 these ergot alkaloids is contraindicated (see Contraindications).

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

HIMG-LOA REQUICIASE Inflibitors (statuts).

Concomitant use of clarithromyticn with lovastatin or sinvastatin is contraindicated (see Contraindications) as these statins are extensively metabolised by CYP3A4 and concomitant treatment with clarithromytin 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 sinvastatin 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.

Effects of other medicinal products on clarithromycin

Entests of other medicinal products on clarithromyclin
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 ZP3A4 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 active substances are known or suspected to affect circulating concentrations of clarithromycin clarithromycin dose 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 14-0H-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological
activities of clarithromycin and 14-0H-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-darithromycin, were increased. Because 14-OH-darithromycin 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 darithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum darithromycin concentration (C_{min}) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14-0H-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 darithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin C_{max} increased by 37%. C_{min} increased 182% and AUC increased by 17% the concentration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dose reduction should be necessary in patients with rormal renal function. However, for patients with renal impairment, the following dose adjustments should be considered: For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} 300 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1g/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 medicinal product interactions).

Effect of clarithromycin on other medicinal products

CYP3A-based interactions

Co-administration of clarithromycin, known to inhibit CYP3A, and an active substance primarily metabolised by CYP3A may be associated with elevations in active substance concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant medicinal product. Granules of the oral suspension can cause a bitter aftertaste when remaining in the mouth. This can be avoided by

The use of clarithromycin is contraindicated in patients receiving the CYP3A substrates astemizole cisapride,domperidone, pimozide and terfenadine due to the risk of OT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see Contraindications and Special warnings and precautions: for use). The use of clarithromycin is also contraindicated with ergot alkaloids, oral midazodam, HMG CoA reductase inhibitors metabolised mainly by CYP3A4 (e.g. lovastatin and simvastatin), colchicine, ticagrelor and ranolazine (see

Clarithromycin should be used with caution in patients receiving treatment with other medicinal products 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.

The following active substances or substance classes are known or suspected to be metabolised by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, ibrutinib, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, see Special warnings and precautions for use) atypical antipsychotics (e.g. quetapine), pimozide, quinidine, futin, isldenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine, but this list is not comprehensive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

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;

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 1_{rg} 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.

afil. tadalafil. and vardenafil
f these phosphodiesterase inhibitors is metabolised, at least in part, by CYP3A, and CYP3A may be inhibited by
intantly administered darithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil
likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil

doses should be considered when these medicinal products are co-administered with clarithro

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

Industroating
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 dose may be necessary in the presence of CYP3A inhibitors, such as clariflyromycin in the CYP2D6 poor metaboliser population.

<u>Triazolobenzodiazepines (e.g. alprazolam. midazolam. triazolam)</u>
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 dosely monitored to allow dose adjustment. Active substance delivery of midazolam via oromucosal rordue, which could bypass pre-systemic elimination of the active substance, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration.

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 medicinal product 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
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 darithromycin may lead to increased exposure to colchicine (see Contraindications
and Special warnings and precautions for use).

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.

Phenytoin and valproate

Zidovudine
Simultaneous oral administration of darithromycin 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 darithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with medicinal products not thought to be metabolised by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these medicinal products when administered concomitantly with clarithromycin. Increased serum Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional

medicinal product 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-clarithromy cally) resulted in a 2-loot increase in exposure to detail results of a 70% decrease in exposure to 14-07-dearmony; in, with a 28% increase in the AUC of atazanavir. Because of the large therapeutic window for darithrom, no dose 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 <00 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 profases inhibitors.

Calcium channel blockers ing the concomitant administration of clarithromycin and calcium channel blockers metabolised Caution is advised regarding the concomitant administration of dariantonity and valuation and valuation of the polytopen son. Plasma concentrations of clarithromy-cin as well as calcium channel blockers may increase due to the interaction. Hypotension, pradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly. Itraconazole

Both darithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bi-directional medicinal product 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.

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional medicinal product interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (sepatatin 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}.

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values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two medicinal products are co-administered for a limited time at the doses/formulations studied. Observations from the two medicinal products are co-administered for a limited time at the doses/formulations studied. Observations from medicinal product interaction studies using the soft gelatin capsule formulation may not be represented of the effects seen using the saquinavir hard gelatin capsule. Observations from medicinal product 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 darithromycin (see Interaction with other medicinal products and other forms of interaction: Ritonavir).

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

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

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

There are no data on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, condusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

Misual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery (section Undesirable effects).

As Summary of the safety profile
The most frequent and common adverse reactions related to clarithromycin therapy for both adult and paediatric populations are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics.

b. Summary of adverse reactions

The following list 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 (±1/10), common (±1/100, common (±1/1,000 to <1/100), and not known (adverse reactions from post-marketing experience; cannot be estimated from the available sull, within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

Blood and lymphatic system disorders

Immune system disorders
Uncommon: Anaphylactoid reaction¹, hypersensitivity
Not known*: Anaphylactic reaction, angioedema

Metabolism and nutrition disorders

Psychiatric disorders

Insomnia
Anxiety, nervousness³
Psychotic disorder, confusional state⁵, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania

Nervous system disorders.
Common:
Uncommon:
Vot known*:
Convalor
Vot known*:
Uncommon:
Vot known*:
Convulsion, ageusia, parosmia, anosmia, paraesthesia

Uncommon: Vertigo, hearing impaired, tinnitus Not known*: Deafness

Cardiac disorders

Uncommon: Cardiac arrest¹, atrial fibrillation¹, electrocardiogram QT prolonged, extrasystoles¹, palpitations Not known*: Torsade de pointes, ventricular tachycardia, ventricular fibrillation

Respiratory, thoracic and mediastinal disorders
Uncommon: Asthma¹, epistaxis², pulmonary embolism¹

Hepatobiliary disorders

Common: Liver function test abnormal
Uncommon: Cholestasis⁴, hepatitis⁴, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased⁴
Not known*: Hepatic failure, jaundice hepatocellular

Skin and subcutaneous tissue disorders

Rash, hyperhidrosis, Dermatitis bullous¹, pruritus, urticaria, rash maculo-papular³ Severe cutaneous adverse reactions (SCAR) (eg: acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia ar systemic symptoms (DRESS)), acne

Musculoskeletal and connective tissue disorders
Uncommon: Muscle spasms³, musculoskeletal stiffness¹, myalgia²
Not known*: Rhabdomyolysis².6, myopathy

:

Renal and urinary disorders

Uncommon:

Not known*:

Blood creatinine increased¹, blood urea increased¹
Renal failure, nephritis interstitial

Common: Injection site pain¹, injection site inflammation¹
Uncommon: Malaise⁴, pyrexia³, asthenia, chest pain⁴, chills⁴, fatigue⁴

dehydrogenase increased*
Not known*: International normalised ratio increased, prothrombin time prolonged, urine colour abnormal

ADRs reported only for the powder for solution for injection formulation

ADRs reported only for the extended-release tablets formulation
ADRs reported only for the granules for oral suspension formulation

ADHs reported only for the granules for oral suspension formulation

4 ADHs reported only for the immediate-release tablets formulation

5-see Description of selected adverse reactions

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 medicinal product exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.

Injection site phlebitis, injection site pain, and injection site inflammation are specific to the clarithromycin intravenous

In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol (see Contraindications and Special warnings and precautions for use).

Special population

Adverse Reactions in immunocompromised patients (see section Other special populations)

Clinical trials have been conducted using darithromycin 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

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

adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 1000 d 2000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulen adache, constipation, hearing disturbance, serum glutamic oxaloacetic transaminase (SGOT) and serum glutam uvate transaminase (SGPT) elevations. Additional low-frequency events included dyspnoea, insomina and uth. The incidences were comparable for patients treated with 1000 mg and 2000 mg, but were generally about 3 production, of the production of the production

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 dose groups also had elevated blood urea nitrogen (BUN) levels. Slightly higher incidences of abnormal values were noted for patients who received 4000 mg daily for all parameters except white blood cell.

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, hypokadaemia, and hypoxaemia.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, macrolides, lincosamides and streptogramins, macrolides
ATC code: JOIFA09

Clarithromycin, a semi-synthetic derivative of erythromycin, exerts its anti-bacterial 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 darithromycin 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 Haemophillus influenzae where the 14-hydroxy metabolite is two-fold more active than the parent compound.

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 (TMIC) 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.

Mechanism of resistance

Resistance mechanisms against macrolide antibiotics include alteration of the target site of the antibiotic or are based on the modification and/or active efflux of the antibiotic.

: Resistance development can be mediated via chromosomes or plasmids, be induced to 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 streptogramine 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 and oxacillin-resistant staphylococci (MRSA) and penicillin-resistant Streptococcus pneumoniae are resistant to all currently available Beta-lactam antibiotics and macrolides such as clarithromycin.

The following breakpoints for clarithromycin, separating susceptible organisms from resis established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST) Pathogens

1 Erythromycin can be used to determine susceptibility to azithromycin, clarithromycin and roxithromycin.
2 Clinical evidence for the efficacy of macrolides in *H. influenzae* respiratory infections is conflicting due to high spontaneous cure rates. Should there be a need to test any macrolide against this species, the epidemiological cut-offs: (ECOFFs) should be used to detect strains with acquired resistance. The ECOFFs for each agent are: azithromycin 4 mg/L, clarithromycin 32 mg/L, erythromycin 16 mg/L and telithromycin 8 mg/L. There are insufficient data available to establish an ECOFF for roxithromycin.
3 The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wikt-type isolates from those with reduced susceptibility.
4 Enthromycin as a he used to determine susceptibility.

4 Erythromycin can be used to determine susceptibility to azithromycin and clarithromycin.
5 Susceptibility can be inferred from erythromycin susceptibility.
El Indicates that there is insufficient evidence that the organism or group is a good target for therapy with the agent. An MIC with a comment but without an accompanying S, I or R categorisation may be reported.

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:

	sceptible species positive microorganisms
/ torobic ordin	Corynebacterium diphtheriae
	Streptococcus Group F
Aorobio Gram	negative microorganisms
Aelobic Oldiin	Bordetella pertussis
	Legionella spp.
	Moraxella catarrhalis
	Pasteurella multorida
Anaerobes	r asieoretia iliutiocida
Alidelopes	Clostridium spp. other than C. difficile
Oil :	
Other microorg	Chlamvdia trachomatis
	Chlamydia pneumoniae
	Clamydophila psittaci Mycoplasma pneumoniae
	Mycobacterium spp.
	hich acquired resistance may be a problem
Aerobic Gram-	positive microorganisms Enterococcus spp.+
	Staphylococcus aureus (methicillin-susceptible and methicillin-resistant+ Staphylococcus epidermidis+
	Streptococcus Group A*, B, C, G
	Streptococcus Group A , B, C, G Streptococcus viridans
	Streptococcus viriaans
	Streptococcus pneumoniae*+
Aerobic Gram-	negative microorganisms Haemophilus influenzae [§]
	Helicobacter pylori
Anaerobes	
	Bacteroides spp.
	Peptococcus/Peptostreptococcus spp.
	sistant organisms
Aerobic Gram-	negative microorganisms
	Acinetobacter
	Enterobacteriaceae
	Pseudomonas aeruginosa
Anaerobes	
	Fusobacterium spp.

disorders

Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain

Desophagitis¹, gastroesophageal reflux disease², gastritis, proctalgia², stomatitis, glossitis, abdominal distension⁴, constipation, dry mouth, eructation, flatulence

Pancreatitis acute, tongue discolouration, tooth discoloration

≥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/recion(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 gastro-doudenal ulcers. As expected, significantly lower eradication rates were observed in patients with baseline metronidazole-resistant H. pylori isolates.

significantly lower eradication rates were observed in patients with baseline metronidazoler-esistant H. Dylon 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. pyloni eradication therapy. Furthermore, in patients with persistent infection, potential development of secondary resistance (in patients with primary susceptible strains) to an antimicrobial medicinal product should be taken into the considerations for a new treatment regimen.

cin is rapidly and well absorbed from the gastrointestinal tract – primarily in the jejunum - but undergoes; irst-pass metabolism after oral administration. The absolute bioavailability of a 250-mg clarithromycin tablet is

The bioavailability of the suspension is identical to or slightly higher than the bioavailability of the tablets. The pharmacokinetic profile of the suspension in children corresponds to the pharmacokinetic profile of the suspension in

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 (60–Methylerythromycin), clarithromycin is quite resistant to degradation by stomach acid. Peak plasma levels of $1-2\,\mu g/mL$ clarithromycin were observed in adults after oral administration of 250 mg darithromycin twice daily the peak plasma level was:

In children the following steady-state parameters were observed after the ninth dose in a dose regimen of 7.5 mg/kg twice daily on average for clarithromycin: C_{\max} 4.60 μg/mL, AUC 15.7 μg-hour/mL and T_{\max} 2.8 hours. The corresponding average values for the 14-OH metabolite were respectively: 1.64 μg/mL, 6.69 μg/hour/mL and 2.7 hours.

After administration of 250 mg clarithromycin twice daily, the microbiologically active 14-hydroxy metabolite attains peak plasma concentrations of $0.6\,\mu g/mL$. 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 bigher than the circulating level of the active substance. Increased levels have been found in both tonsils and lung tissue. Carithromycin also penetrates the:

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

The pharmacokinetics of clarithromycin is non-linear due to saturation of hepatic metabolism at high doses. 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.

Approximately 20 ~40% of clarithromycin is excreted as the unchanged active substance in the urine. This proportion is increased when the dose is increased. An additional 10% to 15% is excreted in the urine as 14-hydroxy metabolite. The rest is excreted in the faces. Renal insufficiency increases clarithromycin levels in plasma, if the dose is decreased. Total plasma clearance has been estimated to approximately 700 mL/min (11.7 mL/s), with a renal clearance of approximately 170 mL/min (2.8 mL/s).

<u>Special populations</u>
Renal impairment: Reduced renal insufficiency function results in increased plasma levels of clarithromycin and the active metabolite levels in plasma.

n 4-week-studies in animals, toxicity of clarithromycin was found to be related to the dose and to the duration of the reatment. 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 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 (pc) 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%).

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.

Storage
Store at temperatures not exceeding 30°C.

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

125 mg/5 mL Granules for Oral Suspension: HDPE Bottle x 50mL

DATE OF FIRST AUTHORIZATION

Manufactured by: **S.C. Sandoz S.R.L.**, Str. Livezeni NR 7A, Tårgu Mureş, Jud. Mureş, Code 540 472, Romania

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