For the use of a registered medical practitioner or a hospital or a laboratory

Clarithromycin

Hospimycin

1. Name of the medicinal product

Clarithromycin 500 mg (Lyophilized) Powder for Concentrate for Solution for IV Infusion

2. Qualitative and quantitative composition

Each vial contains

Clarithromycin I.P. 500 mg

Lactobionic Acid BP qs (TO adjust pH)

One ampoule containing 10ml of sterile water for injection

When reconstituted and diluted as directed, the final diluted solution contains approximately 2 mg/ml of clarithromycin.

3. Pharmaceutical form

Powder for Concentrate for Solution for Infusion

4. Clinical particulars

4.1 Therapeutic indications

Clarithromycin is indicated when parenteral therapy is required for treatment of infections caused by susceptible organisms in the following conditions (see sections 4.4 and 5.1);

– Acute exacerbation of chronic bronchitis

– Community acquired pneumonia

– Acute bacterial sinusitis (adequately diagnosed)

– Streptococcal pharyngitis and tonsillitis

– Skin and soft tissue infections

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

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

4.2 Posology and method of administration

Method of Administration:

For intravenous use only.

Intravenous therapy may be given for 2 to 5 days and should be changed to oral clarithromycin therapy when appropriate. The total duration of treatment should not exceed more than 14 days. The usual duration of treatment is 6 to 14 days.

Adults: The recommended dosage of Clarithromycin is 1.0 gram daily, divided into two 500 mg doses, appropriately diluted.

Children younger than 12 years: Use of clarithromycin IV is not recommended for children younger than 12 years. Use clarithromycin Paediatric Suspension.

Children older than 12 years: As for adults.

Elderly: As for adults.

Renal Impairment: In patients with renal impairment who have creatinine clearance less than 30 ml/min, the dosage of clarithromycin should be reduced to one half of the normal recommended dose.

Recommended administration:

Clarithromycin should be administered into one of the larger proximal veins as an IV infusion over 60 minutes, using a solution concentration of about 2 mg/ml. Clarithromycin should not be given as a bolus or an intramuscular injection.

4.3 Contraindications

Clarithromycin is contra-indicated in patients with known hypersensitivity to macrolide antibiotic drugs.

Clarithromycin and ergot derivatives should not be co-administered (see section 4.5).

Concomitant administration of clarithromycin and any of the following medicinal products is contraindicated: cisapride, pimozide and terfenadine. Elevated cisapride, pimozide and terfenadine levels have been reported in patients receiving either of these medicinal products and clarithromycin concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes. Similar effects have been observed with concomitant administration of astemizole and other macrolides

4.4 Special warnings and precautions for use

Clarithromycin is principally excreted by the liver and kidney. Caution should be exercised in administering this antibiotic to patients with impaired hepatic and renal function.

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

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

The frequency of resistance to macrolides in the EU among Streptococcus pneumonia, Staphylococus aureus and Streptococcus pyogenes is very variable and local data should be taken into consideration when selecting clarithromycin for the treatment of the listed indications for use.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on clarithromycin

Clarithromycin is metabolised via enzyme CYP3A4. Therefore, strong inhibitors of this enzyme may inhibit clarithromycin metabolism, this results in increased plasma concentrations of clarithromycin.

It has been demonstrated that ritonavir (200 mg of ritonavir three times daily) is an inhibitor of clarithromycin (500 mg twice daily) metabolism, whereas an increase of Cmax, Cmin and AUC in concomitant administration with ritonavir are 31, 182 and 77%, respectively. Formation of the active metabolite 14->R@- hydroxyclarithromycin has been almost completely inhibited. In patients with normal renal function the dose of clarithromycin need not be decreased, however, clarithromycin daily dose must not exceed 1 g. A dose reduction should be considered in patients with renal impairment. In patients with creatinine clearance of 30-60 ml/min (0.5 – 1 ml/s) the dose of clarithromycin should be reduced by 50% and in patients with creatinine clearance of <30 ml/min (<0.5 ml/s) the dose should be reduced by 75%.

Although the plasma concentrations of clarithromycin and omeprazole may be increased when they are administered concurrently, no dose adjustment is necessary. Increased plasma concentrations of clarithromycin may also occur when it is coadministered with antacids or ranitidine.

No adjustment to the dosage is necessary.

CYP3A4 inducers (such as rifampicine, phenytoin, carbamazepine, phenobarbital, products containing St. John Wort) may induce clarithromycin metabolism. This may result in sub-therapeutic levels of clarithromycin which decrease the product´s efficacy. If clarithromycin is clearly indicated, it may be necessary to increase the dose of clarithromycin, and closely monitor its efficacy and safety. Further monitoring of plasma levels of the CYP3A4 inducer may be necessary, because the levels may be increased due to CYP3A4 inhibition by clarithromycin (see also relevant Summary of Product Characteristics of the administered CYP3A4 inducer).

Concomitant administration of rifabutine and clarithromycin has resulted in increased rifabutine levels and decreased clarithromycin levels in serum, and in an increased risk of uveitis.

A 39% reduction in AUC for clarithromycin and a 34% increase in AUC for the active 14-OHhydroxy metabolite have been seen when clarithromycin was used concomitantly with the CYP3A4 inducer efavirenz.

Effects of clarithromycin on other medicinal products

Clarithromycin is an inhibitor of metabolising enzyme CYP3A4 and transport Pglycoprotein.

The inhibition level for various CYP3A4 substrates is very difficult to predict. Therefore, clarithromycin should not be used during treatment with other medicinal products which are CYP3A4 substrates, unless their plasma levels, therapeutic effects, or adverse effects of the CYP3A4 substrate can be closely monitored. Medicinal products which are CYP3A4 substrates and are given concomitantly with clarithromycin may require a dose reduction. Alternatively, treatment with these medicinal products may be interrupted during the treatment with clarithromycin.

Medicinal products which may prolong QT interval

Clarithromycin is considered to be an inhibitor of cisapride and terfenadine metabolism with a twofold up to three-fold increase of terfenadine plasma levels. The latter is associated with a QT interval prolongation and heart arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Similar symptoms have been reported in patients who were treated with

pimozide in combination with clarithromycin. Concomitant administration of clarithromycin and terfenadine, cisapride, pimozide and astemizole is contraindicated (see section 4.3).

Torsades de pointes have been reported in patients who were concomitantly receiving clarithromycin and quinidine or disopyramid. Therefore, these combinations must be avoided, or quinidine or disopyramid plasma levels must be closely monitored. A dose adjustment may be necessary. If clarithromycin is given to patients who are treated with other products which may prolong QT interval, cautions should be exercised (see section 4.4).

Ergot vasoconstrictors (e.g. dihydroergotamin, ergotamin)

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

HMG-CoA reductase inhibitors

Clarithromycin is an inhibitor of metabolism of some HMG-CoA reductase inhibitors, this results in an increase of plasma concentrations of these substances.

Rarely, rhabdomyolysis together with increased plasma concentrations have been reported in patients receiving clarithromycin and simvastatin or lovastatin. Clarithromycin may cause similar interactions with atorvastatin. If clarithromycin treatment is indicated in patients treated with simvastatin, lovastatin, or atorvastatin, those patients must be monitored for occurrence of signs of myopathy.

Benzodiazepines

In concomitant administration of midazolam with clarithromycin tablets (250 mg twice daily), AUC of midazolam has increased 2.7-fold and 7-fold following intravenous administration and following oral administration of midazolam, respectively. Concomitant administration of midazolam tablets and clarithromycin should be avoided. In intravenous concomitant administration of midazolam and clarithromycin, the patient should be closely monitored. A dose adjustment may be necessary. The same precautions should also be applied while using other benzodiazepines metabolised via CYP3A4, in particular triazolam as well as alprazolam. An interaction with clarithromycin is unlikely in benzodiazepines which are not metabolised via CYP3A4 (temazepam, nitrazepam, lorazepam).

Cyclosporin, tacrolimus and sirolimus

Concomitant administration of the oral form of clarithromycin with cyclosporin or tacrolimus results an in more than two-fold increase of Cmin plasma concentrations of cyclosporin and tacrolimus. Similar effects can also be expected with sirolimus.

Plasma levels of cyclosporin, tacrolimus or sirolimus should be thoroughly monitored when commencing treatment with clarithromycin in patients on any of the abovementioned immunosuppresants, and their doses should be decreased, if necessary.

Clarithromycin discontinuation in those patients also requires a thorough monitoring of cyclosporin, tacrolimus or sirolimus plasma levels to guide dose adjustment.

Medicinal products transported by P-glycoprotein

Clarithromycin is a potent inhibitor of the transport protein P-glycoprotein (Pgp).This could give rise to increased plasma concentrations of active substances which are transported by this transporter

and may also increase distribution of such active substances to organs having Pgp as an distribution barrier e.g. CNS.

The concentration of the Pgp substrate digoxin may be increased when co- administered with clarithromycin. Monitoring of plasma levels of digoxin should be considered when co-treatment with clarithromycin is initiated or terminated since a dose adjustment may be warranted.

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity

Theophylline

Clarithromycin administration to patients on theophylline is associated with an increase of theophylline serum concentration, and potential theophylline toxicity

Warfarin

The use of Clarithromycin in patients receiving warfarin may result in a potentiation of the effects of warfarin. Prothrombin time should be frequently monitored in these patients.

Zidovudine

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV infected adults may result in decreased steady-state zidovudine concentrations. Since this interaction in adults is thought to be due to interference of clarithromycin with simultaneously administered oral zidovudine, this interaction should not be a problem when clarithromycin is administered intravenously. With oral clarithromycin, the interaction can be largely avoided by staggering the doses; see Summary of Product Characteristics for Clarithromycin tablets for further information. No similar reaction has been reported in children.

The use of clarithromycin in patients concurrently taking other drugs metabolized by the cytochrome p450 system (e.g. cilostazol, methylprednisolone, sildenafil, vinblastine) may be associated with elevations in serum levels of these other medicinal products.

Clarithromycin has been shown not to interact with oral contraceptives.

4.6 Pregnancy and lactation

The safety of Clarithromycin during pregnancy and breast feeding of infants has not been established. Clarithromycin should thus not be used during pregnancy or lactation unless the benefit is considered to outweigh the risk.

Data on the use of clarithromycin during the first trimester of more than 200 pregnancies show no clear evidence of teratogenic effects or adverse effects on the health of the neonate. Data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of abortions. To date no other relevant epidemiological data are available.

Data from animal studies have shown reproductive toxicity. The risk for humans is unknown. Clarithromycin should not be given to pregnant women unless it is clearly needed.

Lactation

Clarithromycin and its active metabolite are excreted in breast milk. Therefore, diarrhoea and fungus infection of the mucous membranes could occur in the breast- fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind. The benefit of treatment of the mother should be weighed against the potential risk for the infant.

4.7 Effects on ability to drive and use machines

Clarithromycin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The undesirable effects have been reported in more than isolated cases, they are listed below according to their organ system and frequency.

The frequency is defined using the following convention:

• Very common (> 1/10)

• Common (> 1/100, < 1/10)

• Uncommon (> 1/1,000, < 1/100)

• Rare (> 1/10,000, < 1/1,000)

• Very rare (< 1/10,000), including isolated cases

Infections and infestations Common (>1/100 and <1/10)	Oral candidiasis.
Blood and lymphatic system disorders Uncommon (>1/1000 and <1/100) Rare (>1/10,000 and <1/1000)	Leucopoenia. Thrombocytopenia.
Immune system disorders Uncommon (>1/1000 and <1/100)	Allergic reactions ranging from exanthema/ urticaria to severe anaphylactic reaction.
Metabolism and nutrition disorders Rare (>1/10,000 and <1/1000)	Hypoglycaemia*, in particular in concomitant administration of antidiabetic agents and insulin.
Psychiatric disorders Very rare (<1/10.000, including isolated cases)	Anxiety, insomnia, hallucinations, psychoses, disorientation, depersonalisation, unpleasant dreams, confusion.
Nervous system disorders Common (>1/100 and <1/10) Rare (>1/10,000 and <1/1000) Very rare (<1/10,000, including isolated cases)	Headache. Altered sense of smell. Convulsions. Muzziness, dizziness, paresthesias.
Ear and labyrinth disorders Rare (>1/10,000 and <1/1000)	Tinnitus. Reversible hearing loss.
Cardiac disorders Rare (>1/10,000 and <1/1000)	Extended QT interval, ventricular tachycardia, Torsades de Pointes.

Vascular disorders Common (>1/100 and <1/10)	Phlebitis.
Gastrointestinal disorders Common (>1/100 and <1/10) Very rare (<1/10,000, including isolated cases)	Nausea, diarrhoea, vomiting, dyspepsia, abdominal pains, reversible discoloration of teeth and tongue, glossitis, stomatitis, taste disorders. Pancreatitis. Pseudomembranous colitis.
Hepatobiliary disorders Uncommon (>1/1000 and <1/100) Very rare (<1/10,000, including isolated cases)	Hepatic dysfunction (normally transient and reversible). Hepatitis. Cholestasis. Icterus. Fatal hepatic insufficiency (particularly in patients with pre- existent liver disease or patients who are undergoing treatment with other hepatotoxic preparations)
Skin and subcutaneous tissue disorders Uncommon (>1/1000 and <1/100) Very rare (<1/10,000, including isolated cases)	Exanthema. Urticaria. Stevens-Johnson's disease, toxic epidermal necrolysis.
Musculoskeletal, connective tissue disorders Uncommon (>1/1000 and <1/100)	Arthralgia, myalgia.
Renal and urinary disorders Very rare (<1/10,000, including isolated cases)	Interstitial nephritis, renal insufficiency.
General disorders and administration site conditions Common (>1/100 and <1/10)	Tenderness at site of administration.
Investigations Common (>1/100 and <1/10) Uncommon (>1/1000 and <1/100)	Increased blood urea nitrogen Extended prothrombin time (increased INR). Increased plasma creatinine. Increased liver transaminases.

4.9 Overdose

There is no experience of overdose after intravenous administration of clarithromycin. However, reports indicate that the ingestion of large amounts of clarithromycin orally can be expected to produce gastro-intestinal symptoms. Adverse reactions accompanying overdose should be treated by gastric lavage and supportive measures.

Clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Macrolides

Mode of action

The mechanism of action of clarithromycin is based on the inhibition of the protein biosynthesis by its binding to the 50S subunit of the bacterial ribosome.

The 14(R)-hydroxy metabolite of clarithromycin, a product of the metabolisation of the parent substance which is found in humans, also has an antibacterial effect. The MICs of this metabolite are equal or twofold 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

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 to clarithromycin can be based on the following mechanisms:

• Target site modification: (conferred by the ermB gene) As a result of the methylation of 23S rRNS, the affinity for the ribosomal binding sites is reduced, leading to high- level macrolide resistance to macrolides (M) and cross reference to lincosamides (L) and Group B streptograms (S_B) (so called MLS_B phenotype);

• Active drug efflux: Resistance can be caused as a result of an increase in the number of active efflux pumps in the cytoplasmic membrane (so-called M phenotype); active drug efflux among pneumococci is mediated by a membrane efflux pump encoded by the *mefA* gene. This mechanism results in low to mid- level resistance.

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). Macrolides administered intravenously are active against *Legionella pneumophila*(erythromycin MIC ≤1 mg/L for wild type isolates). Macrolides have been used in the treatment of infections with*Campylobacter jejuni* (erythromycin MIC ≤4 mg/L for wild type isolates). Azithromycin has been used in the treatment of infections with *S. typhi* (MIC ≤16 mg/L for wild type isolates) and *Shigella* spp.

C. Clarithromycin is used for the eradication of *H. pylori* (MIC ≤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.

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 increased is such that the utility of the agent in at least in some types of infections is questionable.

1. Commonly susceptible species
Aerobic Gram-negative micro-organisms
Haemophilus influenzae[$]
Moraxella catarrhalis
Other micro-organisms
Chlamydophila pneumoniae°
Legionella pneumophila°
Mycoplasma pneumoniae°
2. Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms
Staphylococcus aureus (methicillin-sensitive)
Staphylococcus aureus (methicillin-resistant)[+]
Streptococcus pneumonia
Streptococcus pyogenes [1]
3. Inherently resistant organisms
Aerobic Gram-negative micro-organisms
Escherichia coli
Klebsiella spp.
Pseudomonas aeruginosa

° No actual data were available when the tables were published. Sensitivity is assumed in the primary literature, reference works and treatment recommendations.

[$] The natural sensitivity of most isolates lies in the intermediate range.

[+] The rate of resistance is above 50% in at least one region.

[1] Rate of resistance in some studies ≥10%

5.2 Pharmacokinetic properties

The pharmacokinetics of clarithromycin and the 14-hydroxy metabolite are non- linear; steady state is achieved by day 3 of IV dosing.

Distribution

Clarithromycin penetrates rapidly into various body tissues and fluids. In adults the volume of distribution ranges from 200 to 400 litres. Tissue concentrations in lung and tonsils have been found to be several times higher than the circulating drug levels.

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

Biotransformation and Elimination

Clarithromycin is metabolised in the liver by the cytochrome P-450 enzyme system quickly and to a large extent. The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism as indicated by lower bioavailability of the metabolite following IV administration.

After oral administration of radioactively labeled clarithromycin 70-80% of radioactivity was found in the faeces. About 20-30% of the clarithromycin dose is excreted in the urine in the unchanged form.

In patients with renal impairment an increase of clarithromycin plasma levels and its active metabolite has been observed.

6. Pharmaceutical particulars

6.1 List of excipients

Lactobionic acid

6.2 Incompatibilities

None known. However, Clarithromycin should only be diluted with the diluents recommended. Do not use with diluents containing preservatives or inorganic salts

6.3 Shelf life

36 months unopened.

Reconstituted/Diluted Solutions: Chemical and physical in use stability has been demonstrated for 6 hours at 25°C.

From a microbiological point of view, the reconstituted and diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution /dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

As packaged for sale: Do not store above 30°C. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Clear vial, closed with rubber stopper and aluminium cap. Package is monocarton along with patient information leaflet and one ampoule containing 10ml of sterile water for injection IP.

6.6 Special precautions for disposal and other handling

Clarithromycin should be administered as an intravenous infusion over 60 minutes, using a solution concentration of about 2mg/ml. Clarithromycin should not be given as a bolus or an intramuscular injection.

Dilution:

Prepare all solutions using aseptic techniques.

Step 1: Add 10 ml sterile Water for Injection (PhEur) to the vial to give a 5% initial solution (50 mg/ml). Store at 2 – 8°C.

Step 2: Add 10 ml from step 1 to 250 ml of a suitable diluent to give a final concentration of approximately 2 mg/ml. Store at 2 – 8°C.

IMPORTANT: BOTH DILUENT STEPS SHOULD BE COMPLETED BEFORE USE.

Once reconstituted, the white to off-white caked, lyophilised powder forms a clear solution.

The dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Suitable diluents include:

• Dextrose 50 mg/ml (5%) solution for infusion in Lactated Ringer's Solution

• Dextrose 50 mg/ml (5%) solution for infusion

• Lactated Ringer's Solution

• Dextrose 50 mg/ml (5%) in Sodium Chloride 3 mg/ml (0.3%) solution for infusion

• Dextrose 50 mg/ml (5%) in Sodium Chloride 4.5 mg/ml (0.45%) solution for infusion

• Sodium Chloride 9 mg/ml (0.9%) solution for infusion.

For single use only. Discard any unused solution.

7. Marketed BY:

ALKEM

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