MONOCLARIUM 200 mg, prolonged release capsules.

PHARMACEUTICAL FORM

Prolonged release capsule, yellow/yellow, hard gelatine capsule (size 0)
Each prolonged release capsule contains 200 mg clarithromycin.

Capsule content :

Cellulose microcrystalline, povidone K29/32, citric acid anhydrous, stearic acid.

Pellet coating

Hypromellose, polysorbate 80, talc, titanium dioxide (E171), polyacrylate dispersion 30%.
Antifoam C Emulsion: Dimethicone, Methylated silica, Octamethyl cyclotetrasiloxane, Methylcellulose, Sorbic acid, Benzoic acid.

Capsule shell

Titanium dioxide (E171), quinoline yellow (E104), erythrosine (E127), gelatin.

Pharmacodynamic properties

General properties

ATC classification
Pharmacotherapeutic group: macrolides
ATC Code: J01FA09

Mode 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 suppressing protein synthesis. The 14-hydroxy metabolite of clarithromycin, formed in man by first pass metabolism, 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.

Mechanisms of resistance

Resistance of Gram-positive organisms to the macrolides usually involves an alteration of the antimicrobial binding site. The MLS_B type of resistance, which may be constitutive or induced by exposure to certain macrolides in staphylococci and which is inducible in streptococci, is mediated by a variety of acquired genes (*erm* family) encoding methylases targeted at the peptidyl transferase centre of 23S ribosomal RNA. Methylation impedes binding of antibacterials to the ribosome and gives rise to cross-resistance to macrolides (all macrolides when constitutive), lincosamides and type B streptogramins but not to type A streptogramins. Less frequent mechanisms of resistance include antimicrobial degradation by inactivating enzymes such as esterase and active efflux of the antimicrobial from the bacteria.

Breakpoints

The EUCAST susceptibility testing breakpoints for clarithromycin against streptococci are: Susceptible $\leq$ 0.25 µg/ml; Resistant > 0.5µg/ml.

Susceptibility

Streptococcus pyogenes and other beta-haemolytic streptococci that may be associated with streptococcal infections of the pharynx and tonsils may acquire resistance to clarithromycin as described above. The prevalence of acquired resistance varies geographically but is often more than 10% in the EU and sometimes much higher. See section 4.4.

Pharmacokinetic properties

Absorption

Following oral administration, clarithromycin is rapidly absorbed from the gastrointestinal tract. The absolute bioavailability of clarithromycin is approximately 50% when administered orally.

Food slightly delays the absorption, but has no effect on the extent of bioavailability, and therefore clarithromycin may be given without regard to food.

When Clarium prolonged release capsules were given 400 mg once daily, the peak plasma concentrations of clarithromycin were 0.4–1.2 μg/ml and those of 14-hydroxy clarithromycin 0.2–0.5 μg/ml. Steady state concentrations are reached within 2 to 3 days of the initiation of administration.

Distribution

The tissue concentrations of clarithromycin are several times higher than those occurring in circulation. Increased concentrations have been observed in both the tonsils and lung tissue. Clarithromycin penetrates the labyrinth fluid in higher concentrations than those in serum. Clarithromycin also penetrates well the gastric mucus. At therapeutic levels, 80% of clarithromycin is bound to plasma proteins.

Metabolism

Clarithromycin is rapidly metabolised in the liver (cytochrome P450).

Three clarithromycin metabolites can be observed in the body. N-desmethyl clarithromycin, descladinosyl clarithromycin and 14-hydroxy clarithromycin.

In humans, 14-hydroxy clarithromycin is the main metabolite of clarithromycin. It has antimicrobial action.

Elimination

The elimination half-life of clarithromycin taken once daily is 11 to 14 hours. The half-life of its active metabolite is 14 to 16 hours.

After oral administration of radioactive clarithromycin, 70 to 80% of its radioactivity could be measured in the faeces. Approximately 20 to 30% of clarithromycin is excreted in the urine as unchanged active substances. Renal impairment increases plasma clarithromycin concentrations, if the dose is not reduced.

Total plasma clearance has been estimated to be approximately 700 ml/min with renal clearance approximately 170 ml/min.

THERAPEUTIC INDICATIONS

MONOCLARIUM is indicated for the treatment of the following infections, when caused by clarithromycin susceptible bacteria and only when the patient is known to have hypersensitivity to penicillin or if penicillin is contraindicated for other reasons.

- Streptococcal pyogenes pharyngitis and pharyngotonsillitis

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

POSOLOGY AND METHOD OF ADMINISTRATION

For oral use

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

Adults and adolescents
In patients of 15 years and older, according to the indication, the treatment regimen will be:
- *Tonsillitis/pharyngitis caused by Streptococcus pyogenes:* Two 200 mg capsules once a day.
For the treatment of Streptococcus pyogenes infections (caused by a group A betahemolytic streptococcus), the usual duration of treatment is between 5 and 10 days; official guidelines on the appropriate antibacterial medications should be considered.

Children:
MONOCLARIUM prolonged release capsules is not recommended for use in children below 15 years of age due to lack of data on safety and efficacy.

Elderly:
As for adults

Impaired renal function:
No dosage adjustment is necessary in patients with mild or moderate renal impairment. MONOCLARIUM is not recommended as first choice in patients with severe renal impairment (creatinine clearance <30ml/min) or patients with both severe renal impairment and co-existing hepatic impairment, due to lack of data on safety and efficacy on this population

Impaired hepatic function:
Clinical trials with patients with hepatic impairment have shown that no dose adjustment is required in patients with moderate or severe hepatic impairment, if their renal function is normal. (see also section 4.4).

Method of administration:
The prolonged release capsules should be swallowed with a sufficient amount of fluid (e.g. one glass of water) with meals.
If the patient has difficulty in swallowing, MONOCLARIUM capsules may be opened carefully and the granules emptied onto a spoon. The spoon with the granules should be placed in the mouth, the granules swallowed, after which the patient should drink a glass of water to rinse the mouth so that all granules are swallowed.
The granules must not be chewed or crushed.

CONTRAINDICATIONS
- MONOCLARIUM prolonged release capsules are contraindicated in patients with hypersensitivity to clarithromycin, other macrolides, azalide group antibiotics or any of the excipients.
- patients using ergot alkaloid derivatives
- patients using medicines containing cisapride, pimozide, astemizole or terfenadine. The concomitant use of clarithromycin has been reported to increase plasma concentrations of cisapride, pimozide and terfenadine. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and *torsades de pointes*. Similar effects have been observed with the concomitant use of astemizole and other macrolides (see section 4.5).
- patients with congenital or acquired QT prolongation (see sections 4.4 and 4.5).

- Concomitant administration with simvastatin or lovastatin. Treatment with these agents should be interrupted during clarithromycin treatment (see section 4.5)
- Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Caution is required when prescribing clarithromycin for Patients who are hypersensitive to lincomycin or clindamycin.

Clarithromycin is primarily excreted via the liver. Clinical trials with patients with hepatic impairment have shown that no dose adjustment is required in patients with moderate or severe hepatic impairment, if their renal function is normal. This medicinal product should be used with caution in patients with hepatic impairment, if they also have renal impairment.
The clarithromycin dose should be reduced in patients with renal impairment, depending on the degree of the impairment (see section 4.2). In elderly patients, the possibility of renal impairment should be considered.

Prolonged or repeated clarithromycin treatment may result in a superinfection caused by resistant organisms. Clarithromycin treatment should be discontinued, if the patient develops superinfection.

Pseudomembraneous colitis has been reported with the use of broad-spectrum antibiotics. Therefore, this diagnosis should be considered, if the patient develops severe diarrhea during or following the use of clarithromycin. Clarithromycin treatment should be terminated and the patient should be started on appropriate treatment. The use of drugs causing paralysis of intestine peristaltics is contraindicated.

Other macrolides are known to cause exacerbation of myasthenia gravis. Clarithromycin may also cause aggravation or exacerbation of this condition, and therefore it should be used with caution in patients with myasthenia gravis.

Due to the risk of prolonged QT interval, clarithromycin should be used with caution in patients with coronary artery disease as well as patients with a history of ventricular arrhythmia, with severe cardiac insufficiency, non-compensated hypokalemia and/or hypomagnesemia or bradycardia (pulse below 50). The use of clarithromycin is contraindicated in patients with congenital or acquired QT prolongation (see sections 4.3 and 4.5).

Caution should be exercised, if clarithromycin is indicated for patients receiving concomitant treatment with a CYP3A4 inducer, because it is possible that clarithromycin concentrations may not reach therapeutic levels (see section 4.5).

Clarithromycin is a CYP3A4 inhibitor, and its concomitant use with drugs primarily metabolised via this enzyme should be considered only when clearly necessary (see section 4.5).

Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these drugs (see section 4.5).

Clarithromycin may affect the plasma concentrations and efficacy of several drugs, and also vice versa. Clarithromycin should not be administered concomitantly with certain other drugs (see section 4.3). Section 4.5 also shows other possible drug interactions, which should be considered when planning the treatment.

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 patients (see Section 4.5)."

Macrolide-resistant S. pyogenes are commonly encountered in some geographical areas. The results of susceptibility testing or, if not available, information on local resistance rates, should be taken into account before initiation of treatment. See section 5.1.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Concomitant use with medicinal products causing QT prolongation. *Torsades de pointes* has been reported in patients receiving concomitant clarithromycin and quinidine or disopyramide. Therefore, these drug combinations should be avoided, or the plasma concentrations of quinidine and disopyramide should be monitored carefully and doses adjusted as necessary.

Caution should be exercised, if clarithromycin is administered to patients using other medication with a potential to prolong QT interval (see section 4.4).

Clarithromycin has been reported to inhibit the metabolism of cisapride and terfenadine, which results in a 2 to 3-fold increase of plasma terfenadine levels. This may result in QT prolongation and arrhythmias, including ventricular tachycardia, ventricular fibrillation and *torsades de pointes*. Similar effects have been reported in patients treated with pimozide, when clarithromycin has been added. The concomitant use of clarithromycin with terfenadine, cisapride, pimozide or astemizole is contraindicated (see section 4.3).

The effect of clarithromycin capsules on other drugs

Clarithromycin inhibits both the metabolism related enzyme CYP3A4 and the transport protein P-glycoprotein. Therefore, clarithromycin should not be used concomitantly with drugs that act as substrates for CYP3A4, unless plasma levels, therapeutic effect and adverse effects of the CYP3A4 substrate can be closely monitored (see also section 4.3). A dose reduction may be necessary for CYP3A4 substrates, if they are used concomitantly with clarithromycin. Alternatively, treatment with these drugs may be discontinued for the duration of clarithromycin treatment.

HMG-CoA reductase inhibitors

Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these medicinal products. Rhabdomyolysis in association with increased plasma concentrations have in rare

cases been reported in patients treated with clarithromycin and simvastatin or lovastatin. Clarithromycin may produce a similar interaction with atorvastatin and a lesser interaction with either cerivastatin. When treatment with clarithromycin is indicated in patients receiving treatment with either simvastatin or lovastatin or atorvastatin or cerivastatin patients should be monitored for signs and symptoms of myopathy.

Vasoconstrictive ergot alkaloids (e.g. dihydroergotamine, ergot amine)
Clarithromycin should not be co-administered with ergot alkaloid derivatives (see section 4.3). Ergotism due to increased plasma levels of ergot alkaloids has been reported.

Benzodiazepines
When midazolam was administered concomitantly with clarithromycin, the AUC of midazolam increased 2.7-fold following intravenous administration and 7-fold following oral administration of midazolam. The concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is administered concomitantly with clarithromycin, the patient should be monitored closely and the dose adjusted as necessary. The same precautions should be followed with other benzodiazepines metabolised via CYP3A4, such as triazolam and alprazolam.

Ciclosporine, tacrolimus and sirolimus
The concomitant use of oral clarithromycin resulted in more than a 2-fold increase of the Cmin levels of both ciclosporine and tacrolimusin. Similar effects can also be expected for plasma sirolimus concentrations, and for this reason plasma concentrations should be monitored closely and ciclosporine, tacrolimus and sirolimus doses adjusted as necessary.

Digoxin and other active substances transported by P-glycoprotein (Pgp):
Clarithromycin is a potent inhibitor of the transport protein by P-glycoprotein (Pgp)
Plasma digoxin concentrations may increase, if it is administered concomitantly with clarithromycin. When initiating or terminating clarithromycin treatment, monitoring of plasma digoxin concentrations for dose adjustment is therefore recommended.

Warfarin
Clarithromycin may potentiate the effects of warfarin. Prothrombin time should therefore be monitored regularly and warfarin dosage adjusted as necessary.

Carbamazepine
Clarithromycin may potentiate the effects of carbamazepine by reducing its rate of excretion.

Theophylline
The concomitant use of clarithromycin and theophylline has been associated with increased serum theophylline levels and potential theophylline toxicity.

Zidovudine
The concomitant use of oral clarithromycin with zidovudine in HIV infected adult patients may result in decreased steady-state zidovudine levels. This can be largely

avoided by allowing an interval of 1 to 2 hours between clarithromycin and zidovudine doses. No such reaction has been reported in children.

Rifabutine
The concomitant administration of rifabutine and clarithromycin increased plasma rifabutine levels, and clarithromycin levels were correspondingly reduced. Rifabutine may increase the risk of uveitis.

Fluconazole
Clarithromycin may increase plasma fluconazole levels.

Anti-diabetic products:
After concomitant administration of clarithromycin with insulin and other anti-diabetic medicinal products hypoglycaemia has been observed

The effect of other drugs on clarithromycin capsules
Clarithromycin is metabolised via the enzyme CYP3A4. Therefore, potent inhibitors of this enzyme may inhibit the metabolism of clarithromycin, which results in increased plasma clarithromycin levels. On the other hand, CYP3A4 enzyme inducers may reduce plasma clarithromycin levels.

CYP3A4 enzyme inhibitors
Ritonavir (200 mg three times daily) has been shown to slow down clarithromycin (500 mg twice daily) metabolism. Clarithromycin C_{max} increased by 31%, C_{min} by 182% and AUC by 77%. The formation of 14-hydroxy metabolite is almost completely inhibited. A dose reduction is probably not required in patients with normal renal function, but the daily dose of clarithromycin should not exceed 660 mg. However, clarithromycin dosage should be reduced in patients with renal impairment. If the creatinine clearance is 30 to 60 ml/min, clarithromycin dosage should be reduced by 50%, and if the creatinine clearance is < 30 ml/min, the highest daily dose should be 200 mg.

Although the plasma clarithromycin and omeprazole levels may increase following concomitant administration, dose adjustment is not required. Increased plasma clarithromycin concentrations may also occur when it is administered concomitantly with antacids or ranitidine. Dose adjustment is not necessary.

CYP3A4 enzyme inducers
CYP3A4 inducers (e.g. rifampicin, rifabutine, phenytoin, carbamazepine, phenobarbital and Hypericum perforatum) may induce the metabolism of clarithromycin. As a result, clarithromycin concentrations may not reach therapeutic levels, which results in reduced clinical efficacy.
When clarithromycin and the CYP3A4 inducer efavirenz were used concomitantly, the AUC of clarithromycin was reduced by 39% whilst the AUC of active 14-OH-metabolite increased by 34%.

In such cases, it might be necessary to increase the clarithromycin dosage, and its efficacy and safety should be monitored closely. It may also be necessary to monitor plasma levels of the said CYP3A4 inducer, which may increase as a result of the CYP3A4 inhibition caused by clarithromycin (please see the Summary of Product Characteristics of the said CYP3A4 inducer for details).

Colchicine
Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity (see Section 4.4).

PREGNANCY AND LACTATION

Pregnancy
Data on the use of clarithromycin during the first trimester of more than 200 pregnancies show no clear evidence of teratogenic effects, or of 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 (see section 5.3). The risk for humans is unknown. Clarithromycin should only be given to pregnant women after a careful benefit/risk assessment.

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 born in mind. The benefit of treatment of the mother should be weighed against the potential risk for the infant.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies on the effects on the ability to drive and use machines have been performed.
When performing these activities, the possibility of adverse effects, such as dizziness, vertigo, confusion and disorientation should be taken into account.

UNDESIRABLE EFFECTS
The most common adverse effects reported in patients using clarithromycin capsules included diarrhea (3%), nausea (3%), alterations in the sense of taste (3%), indigestion (2%), abdominal pain and disorders (2%) and headache (2%).

The following terminologies have been used in order to classify the occurrence of undesirable effects: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000) and very rare (<1/10,000).

Infections and infestations

Common: Oral candidosis. As with other antibiotics, the long term use of clarithromycin may result in the excessive growth of resistant organisms.

Blood and the lymphatic system disorders
Uncommon: Leucopenia.
Very rare: Thrombocytopenia.

Immune system disorders
Uncommon: Allergic reactions, the severity of which varies from urticaria and mild skin symptoms to anaphylaxis.

Psychiatric disorders
Very rare: Anxiety, insomnia, hallucinations, psychosis, disorientation, depersonalisation, nightmares and confusion.

Nervous system disorders
Common: headache, alteration in the sense of smell.
Very rare: dizziness, vertigo, tactile hallucinations, convulsions.

Ear and labyrinth disorders
Rare: tinnitus.
Very rare: Reversible hearing loss.

Cardiac disorders
Very rare: QT prolongation, ventricular tachycardia and *torsades de pointes*.

Gastrointestinal disorders
Common: Nausea, diarrhea, vomiting, abdominal pain, dyspepsia, stomatitis, glossitis, reversible tooth and tongue discolouration and taste perversion, e.g. bitter or metallic taste.
Very rare: Pancreatitis. Clarithromycin treatment has been very rarely associated with reports of pseudomembraneous colitis, which has ranged in severity from mild to life threatening.

Hepato-biliary disorders
Uncommon: Hepatic dysfunction, usually transient and reversible, as well as hepatitis and cholestasis, which may be associated with jaundice.
Very rare: Fatal hepatic impairment has been reported especially in patients with previous hepatic conditions or patients using other hepatotoxic drugs.

Skin and subcutaneous tissue disorders
Very rare: Stevens-Johnson syndrome and toxic epidermal necrolysis.
Musculoskeletal and connective tissue
Uncommon: Arthralgia, myalgia.

Renal and urinary disorders
Very rare: intestinal nephritis, renal failure

Investigations
Common: Elevated BUN
Uncommon: Prolongation of prothrombin time, elevated serum creatinine, altered liver function tests (increased transaminase levels).
Very rare: Hypoglycaemia has been observed especially after concomitant administration with antidiabetic medicinal products and insulin.

OVERDOSE
Symptoms:
Ingestion of large doses of clarithromycin can be expected to cause adverse effects listed in section 4.8, especially gastrointestinal symptoms. Altered mental status, paranoid behaviour, hypokalemia and hypoxemia were observed in a patient with bipolar disorder following the ingestion of an 8 gram dose of clarithromycin.

Treatment:
There is no specific antidote for the treatment of overdose cases. Gastric lavage and support therapy should be initiated. Administration of medicinal charcoal may be beneficial. The removal of non-absorbed drug via gastric lavage may be beneficial, especially with the prolonged release product. Serum clarithromycin levels cannot be reduced via hemodialysis or peritoneal dialysis. Severe acute allergic reactions, such as anaphylactic shocks, may occur very rarely. When the first overdose symptoms occur, clarithromycin should be discontinued and the required treatment measures initiated without delay.

SHELF LIFE
3 years.

STORAGE
Do not store above 25°C.

NATURE AND CONTENTS OF CONTAINER
PVC-Aclar/ALU blister
10 capsules/blister
Pack sizes: 10 capsules

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