SUMMARY OF PRODUCT CHARACTERISTICS OF CLARICOS 500 MG FILM COATED TABLET

1. Name of the medicinal product

Claricos 500 mg Film Coated Tablet

2. Qualitative and quantitative composition

Each film coated tablet contains 500 mg of Clarithromycin.

3. Pharmaceutical form

Film Coated Tablet

Yellow capsule shaped biconvex film coated, tablet embossed '500' on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

It is indicated for the treatment of the following bacterial infections.

• Bacterial pharyngitis

• Mild to moderate community acquired pneumonia

• Acute bacterial sinusitis (adequately diagnosed)

• Acute exacerbation of chronic bronchitis

• Skin infections and soft tissue infections of mild to moderate severity,

• In appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing agent for the eradication of Helicobacter pylori in patients with Helicobacter pylori associated ulcers

4.2 Posology and method of administration

Posology

The dosage of Clarithromycin film-coated tablets depends on the type and severity of the infection and has to be defined in any case by the physician.

Adults and adolescents (12 years and older)

• Standard dosage: The usual dose is 250 mg twice daily (in the morning and in the evening)

• High dosage treatment (severe infections): The usual dose may be increased to 500 mg twice daily in severe infections.

Children younger than 12 years:

Use of Clarithromycin film-coated tablets is not recommended for children younger than 12 years with a body weight less than 30 kg. Clinical trials have been conducted using clarithromycin pediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension.

For children with a body weight of more than 30kg, the dose for adults apply.

Dosage in renal functional impairment:

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

Patients with hepatic impairment:

Caution should be exercised when administrating clarithromycin in patients with hepatic impairment.

H. pylori eradication in peptic ulcer disease

For the eradication of *H. pylori* the selection of antibiotics should consider the individual patient's drug tolerance, and should be undertaken in accordance with national, regional and local resistance patterns and treatment guidelines.

Usually clarithromycin is administered in combination with another antibiotic and a proton-pump inhibitor for one week.

The therapy may be repeated if the patient is still H. pylori-positive

Duration of therapy:

The duration of therapy with Clarithromycin film-coated tablets depends on the type and severity of the infection and has to be defined in any case by the physician.

• The usual duration of treatment is 7 to 14 days.
• Therapy should be continued at least for 2 days after symptoms have subsided.

• In Streptococcus pyogenes (group A beta-haemolytic streptococcus) infections the duration of therapy should be at least 10 days.

4.3 Contraindications

Clarithromycin is contraindicated in patients with known hypersensitivity to the active substance clarithromycin, to other macrolides or to any of the excipients.

Concomitant administration of clarithromycin and any of the following active substances is contraindicated: astemizole, cisapride, pimozide and terfenadine as this may result in QT prolongation (congenital or documented acquired QT prolongation) and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes (see section 4.5).

Concomitant administration with ticagrelor or renolazine is contraindicated.

Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated, as this may result in ergot toxicity.

Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointe.

Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolosed by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.

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 impairment.

As with other strong CYP3A4 inhibitors, Clarithromycin should not be used in patients taking colchicine.

4.4 Special warnings and precautions for use

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

Caution is advised in patients with severe renal insufficiency.

Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.

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

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 diarrhea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of C.difficile. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

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. Concomitant administration of clarithromycin and colchicines is contraindicated.

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and midazolam.

4.5 Interaction with other medicinal products and other forms of interaction

Cisapride, pimozide, astemizole and terfenadine

Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly.

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

Ergotamine/dihydroergotamine

Postmarketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated.

HMG-CoA Reductase Inhibitors (statins)

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

4.6 Pregnancy and lactation

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.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Infections and infestations			Cellulitis, candidiasis, gastroenteritis, infection, vaginal infection	Pseudomembranous colitis, erysipelas
Blood and lymphatic system			Leukopenia, neutropenia, thrombocythemia, eosinophilia	Agranulocytosis, thrombocytopenia
Immune system disorders[5]			Anaphylactoid reaction, Hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	

Psychiatric disorders		Insomnia	Anxiety, nervousness	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal
				dreams, mania
Nervous system disorders		Dysgeusia, headache, taste perversion	Loss of consciousness, dyskinesia, dizziness, somnolence, tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing, impaired, tinnitus	Deafness

4.9 Overdose

Symptoms of intoxication:

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 eight grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxemia.

Therapy of intoxication:

Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

In the case of overdosage, clarithromycin IV (powder for solution for injection) should be discontinued and all other appropriate supportive measures should be instituted.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible

bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram- negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.

The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or 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.

5.2 Pharmacokinetic properties

Absorption:

Clarithromycin is rapidly and well absorbed from the gastrointestinal tract – primarily in the jejunum – but undergoes extensive first-pass metabolism after oral administration. The absolute bioavailability of a 250-mg clarithromycin tablet is approximately 50%. Food slightly delays the absorption but does not affect the extent of bioavailability. Therefore, clarithromycin tablets may be given without regard to food. Due to its chemical structure (6-O-Methylerythromycin) clarithromycin is quite resistant to degradation by stomach acid. Peak plasma levels of 1 – 2 μg/ml clarithromycin were observed in adults after oral administration of 250 mg twice daily. After administration of 500 mg clarithromycin twice daily the peak plasma level was 2.8 μg/ml. After administration of 250 mg clarithromycin twice daily the microbiologically active 14- hydroxy metabolite attains peak plasma concentrations of 0.6 μg/ml. Steady state is attained within 2 days of dosing.

Distribution:

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

Clarithromycin is approximately 70% bound to plasma proteins at therapeutic levels.

Biotransformation and elimination:

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 14-hydroxy clarithromycin. 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.

5.3 Preclinical safety data

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

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 (i.v.) and x10 the clinical dose in monkey (p.o.) resulted in an increased incidence of spontaneous abortions. These doses were related to maternal toxicity. No embryotoxicity or teratogenicity was noted in rat studies. Cardiovascular malformations were observed in rats treated with doses of 150 mg/kg/d. In mouse at doses x70 the clinical dose cleft palate occurred at varying incidence (3-30%).

Clarithromycin has been found in the milk of lactating animals.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose BP
Maize starch BP

Crospovidone BP

Povidone BP
Potassium sorbate BP

Maize Starch BP (For Paste)

Purified Water BP

Magnesium stearate BP

Maize Starch BP (Dried)

Crospovidone BP

Microcrystalline Cellulose BP (Dried)

Purified Talc BP

Sodium Starch Glycolate BP

FILM COATING

Hypromellose BP
Macrogol 300 BP

Titanium Dioxide BP

Quinoline Yellow Lake

Isopropyl Alcohol

Dichloromethane BP

Carnauba Wax

Hard Paraffin

Chloroform BP

6.2 Incompatibilities

None known

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a dry place below 30˚C. Protect from light.

Keep all medicines out of the reach of children.

6.5 Nature and contents of container

PVDC/Aluminium foil, Packs of 14 Tablets in a carton

6.6 Special precautions for disposal and other handling

Not applicable.

7 Registrant

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8 Manufacturer

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