1.5.5 Proposed Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

KLARITHRAN MR 500 (TABLET)

Contains sugar: Lactose monohydrate 127,80 mg per tablet

For full list of excipients, see section 6.1

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains clarithromycin 500 mg

Sugar free

3. PHARMACEUTICAL FORM

Tablet

Pale yellow coloured, oval, biconvex, film coated tablets printed with ‘CLNXL’ in black ink on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KLARITHRAN MR 500 is indicated for the treatment of the following mild to moderately severe infections caused by susceptible organisms:

- Lower respiratory tract infections such as bronchitis and pneumonia.
- Upper respiratory tract infections such as pharyngitis and sinusitis.
- Mild to moderately severe acute otitis media due to *S. pneumoniae, M. catarrhalis* and *H. influenza.*

- Skin and soft tissue infections such as folliculitis, cellulitis or erysipelas.
- Eradication of *Helicobacter pylori* when used in combination with a proton pump inhibitor and another antibiotic to decrease recurrence of duodenal ulcer.

4.2 Posology and method of administration

Adults: 500 mg once daily with food.

In more severe infections, the dosage may be increased to

2 x 500 mg once daily.

Renal impairment

Creatinine clearance (<30 ml/min): **Klarithran MR 500** should not be used in patients with significant renal impairment (creatinine clearance less than 30 ml/min). **Klarithran** 250 and 500 mg immediate release tablets may be utilized in this patient population.

Eradication of *H. pylori*

Adults: 2 x 500 mg once daily with food, in combination with an appropriate antibiotic and an acid lowering agent, for 7 to 10 days.

The safety and efficacy of **Klarithran MR 500** in combination with proton-pump inhibitors other than omeprazole has not been established.

Atypical mycobacterial infections (MAC) in HIV patients

Adults: 2 x 500 mg once daily with food.

Treatment of disseminated MAC infections in AIDS patients should continue as long as clinical and microbiological benefit is demonstrated. A decrease in efficacy has been noted in patients taking **KLARITHRAN MR 500** for more than 12 weeks. **KLARITHRAN MR 500** should be used in conjunction with other antimycobacterial agents.

KLARITHRAN MR 500 must be taken with meals.

Method of administration:

Administration is by the oral route.

4.3 Contraindications

- Hypersensitivity to macrolide antibiotics or excipients in listed in section 6.1.
- Concomitant administration of **KLARITHRAN MR 500** with astemizole, cisapride, pimozide and terfenadine (See **Interactions**).
- Porphyria.

4.4 Special warnings and precautions for use

KLARITHRAN MR 500 should be used with caution in:

- Liver function impairment – The pharmacokinetics are altered. No dosage adjustment is required in patients with hepatic function impairment, unless there is also concurrent severe renal function impairment.
- Renal function impairment (severe) – The elimination of **KLARITHRAN MR 500** is reduced in patients with renal function impairment, especially those with a creatinine clearance of < 30 ml/min. The dose of **KLARITHRAN MR 500** should be halved or the dosing interval doubled in patients with a creatinine clearance of < 30 ml/min.
- Rhabdomyolysis has been reported with concomitant use of **KLARITHRAN MR 500** and the HMGCoA reductase inhibitors e.g. simvastatin **(See Section 4.5).**
- Rifabutin and rifampicin – May decrease serum concentration of **KLARITHRAN MR 500** by > 50 %. Co-administration has been reported to cause a higher incidence of uveitis compared to rifabutin alone. **(See Section 4.5).**
- Theophylline – The area under the plasma concentration-time curve is increased. Monitoring of theophylline serum concentrations is recommended **(See Section 4.5).**
- Cross-resistance between **KLARITHRAN MR 500** and other macrolides, lincomycin and clindamycin have been reported.

- Treatment with **KLARITHRAN MR 500** should be discontinued if any signs of hepatic dysfunction develop. Hepatic dysfunction is usually reversible, but may be severe. In rare instances, hepatic failure with fatal outcome has been reported, usually associated with other serious underlying diseases and/or concomitant medicines. Isolated cases of increased serum creatinine have been reported, but an association with **KLARITHRAN MR 500** has not been established.
- There have been less frequent reports of hypoglycaemia, some of which occurred in patients on concomitant oral hypoglycaemics or insulin.
- Adverse effects in immunocompromised patients treated with higher doses of **KLARITHRAN MR 500** over long periods include nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, hearing disturbance, AST (Aspartate aminotransferase) and ALT (Alanine aminotransferease) elevations, elevated BUN (Blood Urea Nitrogen) levels and abnormally low white blood cell and platelet counts. Additional low-frequency events included dyspnoea, insomnia and dry mouth.
- Contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of **KLARITHRAN MR 500** with:

- Astemizole, cisapride, pimozide and terfenadine – Has resulted in cardiac arrhythmias, including QTc-interval prolongation, ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation and torsade de pointes. Fatalities have occurred. The most likely cause is the inhibition of metabolism of these medicines by **KLARITHRAN MR 500**. Concurrent use is contra-indicated. **(See Section 4.3)**
- Anticoagulants such as warfarin – **KLARITHRAN MR 500** may result in the potentiation of the effects of warfarin. Prothrombin time should be monitored closely.

- Digoxin – **KLARITHRAN MR 500** has been shown to increase serum digoxin concentrations. Monitoring of digoxin serum concentrations is recommended.
- Carbamazepine or other medicines metabolised by the cytochrome P450 enzyme system for example, alprazolam, cyclosporine, disopyramide, ergot alkaloids, methylprednisolone, midazolam, omeprazole, quinidine, sildenafil, simvastatin, tacrolimus, triazolam, vinblastine, phenytoin, and valproate – **KLARITHRAN MR 500** may be associated with increased levels of these medicines. Serum concentrations of these medicines may require monitoring.
- Rhabdomyolysis has been reported with concomitant use of **KLARITHRAN MR 500** and the HMGCoA reductase inhibitors e.g. simvastatin **(See Section 4.4).**
- Rifabutin and rifampicin – May decrease serum concentration of **KLARITHRAN MR 500** by >50 %. Co-administration has been reported to cause a higher incidence of uveitis compared to rifabutin alone **(See Section 4.4).**
- Theophylline – The area under the plasma concentration-time curve is increased. Monitoring of theophylline serum concentrations is recommended **(See Section 4.4).**
- Zidovudine – A decrease in the steady-state concentration of zidovudine may occur. Doses of zidovudine and **Klarithran MR 500** should be taken at least 4 hours apart.
- Ritonavir – The metabolism of **Klarithran MR 500** is inhibited. No dosage reduction of **Klarithran MR 500** is needed in patients with normal renal function. Patients with renal function impairment require a reduction in the dosage of **Klarithran MR 500** as follows:

  Creatinine clearance 30 to 60 ml/min – Reduce dose by 50 %.

  Creatinine clearance of <30 ml/min – Reduce dose by 75 %.

  Do not exceed a dose of 1 g/day during concurrent administration of **Klarithran MR 500** with ritonavir.

  It has been suggested that other HIV-protease inhibitors and non-nucleoside reverse transcriptase inhibitors may have a similar effect on **Klarithran MR 500.**

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation have not been established.

KLARITHRAN MR 500 is excreted in the breast milk.

4.7 Effects on ability to drive and use machines

The effects on ability to drive and use machines has not been established.

4.8 Undesirable effects

System Organ Class	**Frequency**	**Adverse Reaction**
Blood and lymphatic system disorders	Less frequent	Leucopenia, thrombocytopenia.
Endocrine disorders	Less frequent	Hypoglycaemia.
Nervous system disorders	Less frequent	Headache, anxiety, dizziness, insomnia, hallucinations, bad dreams, vertigo, tinnitus, disorientation, depersonalisation, confusion, hearing loss, convulsions.
Cardiac disorders		QT prolongation, ventricular tachycardia, torsades de pointes.
Gastro-intestinal disorders	Frequent	Nausea, vomiting, abdominal pain, abnormal taste, diarrhoea.
	Less frequent	Glossitis, stomatitis, oral candidiasis, tongue discolouration, tooth discolouration,

		pseudomembranous colitis (abdominal cramps or pain, tenderness, severe, watery diarrhoea which may also be bloody, fever).
Hepato-biliary disorders	Less frequent	Increase in liver enzymes, hepatocellular and/or cholestatic hepatitis (with or without jaundice), pancreatitis
Skin and subcutaneous tissue disorders	Frequency Unknown	Mild skin eruptions, urticaria, Steven's-Johnson syndrome, toxic epidermal necrolysis.
Other	Frequency Unknown	Allergic reactions, anaphylaxis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Ingestion of large amounts of **Klarithran MR 500** can be expected to produce gastro-intestinal symptoms. Allergic reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed medicine and supportive measures.

Treatment is symptomatic and supportive. **KLARITHRAN MR 500** is not expected to be appreciably affected by haemodialysis or dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use, macrolide

ATC code: J01FA09

Category and Class: A.20.1.1 Broad and medium spectrum antibiotics.

Mechanism of action

Clarithromycin is a macrolide antibiotic. It exerts its antibacterial action by binding reversibly to the 50S ribosomal subunit of the 70S ribosome of sensitive micro organisms, thereby inhibiting bacterial RNA-dependant protein synthesis. The *in vitro* antibacterial spectrum of pathogens sensitive to clarithromycin includes:

(*in vitro* sensitivity does not necessarily imply *in vivo* efficacy)

Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus pneumoniae, Legionella pneumophilia

Mycoplasma pneumoniae

Chlamydia trachomatis

Moraxella (Branhamella) catarrhalis

Haemophilus influenzae

Staphylococcus aureus (methicillin sensitive)

Helicobacter pylori

Mycobacterium avium, Mycobacterium kansasii, Mycobacterium chelonae, Mycobacterium intracellulare

5.2 Pharmacokinetic properties

Clarithromycin is absorbed rapidly from the gastro-intestinal tract after oral administration, but its bioavailability is reduced to 50 % from 55 % because of rapid first-pass metabolism. Peak

plasma concentration occurs approximately 5 to 7 hours after administration. Clarithromycin may be given with or without food. Clarithromycin is metabolised by the liver to the active metabolite, 14-hydroxyclarithromycin, as well as to several other metabolites. Both clarithromycin and 14-hydroxyclarithromycin distribute widely throughout the body and achieve high intracellular concentrations. Tissue concentrations generally exceed serum concentrations. Clarithromycin does not achieve significant levels in the cerebrospinal fluid. Protein binding of clarithromycin ranges from 40 to 70 % and is concentration-dependent. The elimination half-lives of clarithromycin and 14-hydroxyclarithromycin are approximately 3 to 7 and 5 to 9 hours respectively. Longer half-lives are observed after larger doses. Clarithromycin is eliminated by renal and non-renal routes. The amount of clarithromycin excreted unchanged in the urine ranges from 20 to 40 %, depending on the dose administered and the formulation. Between 10 and 15 % of the dose is excreted in the urine as the 14-hydroxy metabolite. Although the pharmacokinetics of clarithromycin are altered in patients with hepatic or renal dysfunction, dosage adjustment is not necessary unless a patient has severe renal dysfunction (creatinine clearance of <30 ml/minute). At higher doses in HIV-infected patients clarithromycin and 14-hydroxyclarithromycin concentrations are much higher when compared with usual doses in non-infected patients. The elimination half-lives also appear to be lengthened.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Intragranular ingredients

- Colloidal anhydrous silica
- Lactose monohydrate (Pharmatose)
- Hydroxypropyl methylcellulose (K15 MCR)
- Microcrystalline cellulose
- Povidone Ph. Eur. (PVP K30)

Extragranular ingredients

- Colloidal anhydrous silica
- Magnesium stearate
- Purified water
- Sodium stearyl fumarate

Film Coating Ingredients

- Opadry 20 H 52875
- Purified water

Imprinting Ingredients

- Opacode S-1 -17823 Black
- Isopropyl alcohol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 °C in the original container protected from moisture.

6.5 Nature and contents of container

5 or 10 tablets packed in blister strips. Blister strips comprise of clear, transparent, PVC film-coated with PVdC, having a backing of plain aluminium foil.

Cartons contain 5 or 10 tablets.

6.6 Special precautions for disposal and other handling

Not applicable.

7 HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

14 LAUTRE ROAD

STORMILL EXT. 1

ROODEPOORT

1724

SOUTH AFRICA

8 REGISTRATION NUMBER(S)

A39/20.1.1/0619 (South Africa)

S2 08/20.1.1/0087 (Namibia)

S2 BOT 0700981 (Botswana)

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December 2006

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27 July 2022