**SCHEDULING STATUS**

S4

## 1. NAME OF THE MEDICINE

**KLARIBIN 125 mg/5 ml**

**KLARIBIN 250 mg/5 ml**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**KLARIBIN 125 mg/5 ml**

Each 5 ml of constituted suspension contains:

| | |
|---|---|
| Clarithromycin | 125 mg |
| Sodium benzoate (as preservative) | 0,2 % m/v |

Contains Sugar:

| | |
|---|---|
| Sucrose | 2,929 g/5 ml |
| Contains Aspartame | 20 mg |

For full list of excipients, see section 6.1

**KLARIBIN 250 mg/5 ml**

Each 5 ml of constituted suspension contains:

| | |
|---|---|
| Clarithromycin | 250 mg |
| Sodium benzoate (as preservative) | 0,2 % m/v |

Contains Sugar:

| | |
|---|---|
| Sucrose | 2,508 g |
| Contains Aspartame | 20 mg |

For full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Suspension

**KLARIBIN 125 mg/5 ml:** White to off-white granular powder forming a white to off-white suspension on constitution with water. The resulting suspension has a sweet taste and fruity flavour.

**KLARIBIN 250 mg/5 ml:** White to off-white granular powder forming a white to off-white suspension on constitution with water. The resulting suspension has a sweet taste and fruity flavour.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**KLARIBIN** 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**

**Children**

Safety and efficacy in infants under 6 months of age has not been established. The recommended dose for children over 6 months is based upon a 7,5 mg/kg dose administered twice daily. See dosage table below.

The usual duration of treatment is 5 to 10 days, depending on the pathogen involved and the severity of infection.

In patients with severe renal function impairment (creatinine clearance <30 ml/min), the dosage of **KLARIBIN** should be reduced by half. Do not continue treatment in these patients for more than 14 days.

**KLARIBIN** may be taken with or without meals and can be taken with milk.

| **Weight** | **Approximate age** | **Dose in ml of 125 mg/5 ml suspension** | **Dose in ml of 250 mg/5 ml suspension** |
|---|---|---|---|
| 8 to 11 kg | 1 to 2 years | 2,5 ml twice daily | - |
| 12 to 19 kg | 2 to 4 years | 5 ml twice daily | 2,5 ml twice daily |
| 20 to 29 kg | 4 to 8 years | 7,5 ml twice daily | 3,75 ml twice daily |
| 30 to 40 kg | 8 to 12 years | 10 ml twice daily | 5 ml twice daily |

**Reconstitution instructions:**

The quantity of distilled water specified for the pack size in the table below should be added to the granules and the contents shaken well.

| Pack size | Volume of water to be added |
|---|---|
| 60 ml | 34 ml |
| 70 ml | 40 ml |
| 100 ml | 55 ml |

**Adults:** 250 mg twice daily.

In more severe infections, the dosage may be increased to 500 mg twice daily.

**Renal impairment**

Creatinine clearance (<30 ml/min): Reduce dose by half i.e. 250 mg once daily or 250 mg twice daily for severe infections. Limit the duration of treatment to 14 days.

**Eradication of *H. pylori***

**Adults:** 500 mg twice daily, in combination with an appropriate antibiotic and an acid lowering agent, for 7 to 10 days.

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

**Atypical mycobacterial infections (MAC) in HIV patients**

**Adults:** 500 mg twice daily

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 **KLARIBIN** for more than 12 weeks. **KLARIBIN** should be used in conjunction with other antimycobacterial agents.

**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 **KLARIBIN** with astemizole, cisapride, pimozide and terfenadine (See **Section 4.5**).
- Porphyria.

**4.4 Special warnings and precautions for use**

**KLARIBIN** 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 **KLARIBIN** is reduced in patients with renal function impairment, especially those with a creatinine clearance of <30 ml/min. The dose of **KLARIBIN** of 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 **KLARIBIN** and the HMGCoA reductase inhibitors e.g. simvastatin (See **Section 4.5**).
- Rifabutin and rifampicin – May decrease serum concentration of **KLARIBIN** 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 **KLARIBIN** and other macrolides, lincomycin and clindamycin have been reported.

Treatment with **KLARIBIN** 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 **KLARIBIN** 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 **KLARIBIN** 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.

**KLARIBIN** contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Aspartame

**KLARIBIN** contains 20 mg Aspartame in each 5 ml which is equivalent 4 mg/ml. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Sodium

**KLARIBIN** contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

**4.5 Interaction with other medicines and other forms of interaction**

Concomitant use of **KLARIBIN** 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 **KLARIBIN**. Concurrent use is contra-indicated. See **Section 4.3**.
- Anticoagulants such as warfarin – **KLARIBIN** may result in the potentiation of the effects of warfarin. Prothrombin time should be monitored closely.
- Digoxin – **KLARIBIN** 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 – **KLARIBIN** 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 **KLARIBIN** and the HMGCoA reductase inhibitors e.g. simvastatin (See **Section 4.4**).
- Rifabutin and rifampicin – May decrease serum concentration of **KLARIBIN** 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 **KLARIBIN** should be taken at least 4 hours apart.
- Ritonavir – The metabolism of **KLARIBIN** is inhibited. No dosage reduction of **KLARIBIN** is needed in patients with normal renal function. Patients with renal function impairment require a reduction in the dosage of **KLARIBIN** 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 **KLARIBIN** with ritonavir.

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

**4.6 Fertility, pregnancy and lactation**

Safety and efficacy in pregnancy and lactation have not been established. **KLARIBIN** 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 | Frequency Unknown | Headache, anxiety, dizziness, insomnia, hallucinations, bad dreams, vertigo, tinnitus, disorientation, depersonalisation, confusion, hearing loss, convulsions. |
| Cardiac disorders | Frequency Unknown | 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 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**

**Symptoms of overdose**

Ingestion of large amounts of **KLARIBIN** 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 of overdose**

Treatment is symptomatic and supportive. **KLARIBIN** 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 2 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 larges 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**

- Alginic acid
- Aspartame
- Carbomer (Carbopol 974 P)
- Colloidal anhydrous silica
- Croscarmellose sodium
- Flavour Peppermint

- Flavour Tutti Frutti 051880 AP0551
- Hydroxypropyl cellulose
- Hypromellose
- Isopropyl alcohol
- Macrogol 1500 (polyethylene glycol)
- Methacrylic acid -ethyl acrylate copolymer (1:1) Dispersion 30 %
- Microcrystalline cellulose
- Monosodium citrate
- Purified water
- Sodium benzoate
- Sodium chloride
- Sucrose
- Titanium dioxide
- Talc
- Xanthan Gum

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

24 Months

**6.4 Special precautions for storage**

**KLARIBIN 125 and 250 mg/5 ml:**

Store at or below 25 °C. Keep the bottle tightly closed. Do not refrigerate or freeze. Discard the unused portion of constituted suspension after 14 days.

SHAKE THE BOTTLE WELL BEFORE USE.

**6.5 Nature and contents of container**

**KLARIBIN 125 mg/5 ml**: Natural translucent HDPE bottle pack of 60 ml, 70 ml and 100 ml.

**KLARIBIN 250 mg/5 ml**: Natural translucent HDPE bottle pack of 60 ml, 70 ml and 100 ml.

**6.6 Special precautions for disposal and other handling**

**Reconstitution instructions:**

The quantity of distilled water specified for the pack size in the table below should be added to the granules and the contents shaken well.

| **Pack size** | **Volume of water to be added** |
|---|---|
| 60 ml | 34 ml |
| 70 ml | 40 ml |
| 100 ml | 55 ml |

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

14 LAUTRE ROAD

STORMILL, EXT 1,

ROODEPOORT, 1724

SOUTH AFRICA

## 8 REGISTRATION NUMBER(S)

**KLARIBIN 125 mg/5 ml**

38/20.1.1/0176 (South Africa)

| | |
|---|---|
| NS2 | 08/20.1.1/0023 (Namibia) |

**KLARIBIN 250 mg/5 ml**

38/20.1.1/0163 (South Africa)

| | |
|---|---|
| NS2 | 08/20.1.1/0041(Namibia) |

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 September 2022

Marketed by Aurobindo Pharma (Pty) Ltd

## 10 DATE OF REVISON OF THE TEXT

28 September 2022