Approved Professional Information for Medicines for Human Use: ERYKO-250

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ERYKO-250 250 mg (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ERYKO-250 250 mg tablets

Each ERYKO-250 film–coated tablet contains erythromycin stearate equivalent to 250 mg erythromycin activity.

Contains sugar (lactose monohydrate).

Each ERYKO-250 250 mg film–coated tablet contains 15 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ERYKO-250 250 mg tablets are pink, ovaloid, slightly biconvex, approximately 21,5 x 8,7 mm (length and width respectively) film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ERYKO - 250 is indicated for the treatment of infections caused by susceptible micro-organisms. Wherever possible, culture and sensitivity tests should be done, and treatment chosen accordingly.

ERYKO - 250 is a broad-spectrum antibiotic with activity against gram-positive and gram-negative bacteria, mycoplasmas, spirochaetes and *Chlamydia trachomatis.*

Upper respiratory tract infections (sinusitis, pharyngitis, acute otitis media)

Caused by sensitive *Streptococcus pyogenes, Streptococcus pneumoniae, Corynebacterium diphtheriae.*

Also indicated for prophylaxis and treatment of streptococcal pharyngitis and long-term prophylaxis of rheumatic fever when penicillin is contraindicated. Treatment for streptococcal pharyngitis should be continued for 10 days.

Lower respiratory tract infections (bronchitis, pneumonia – typical and atypical)

Caused by sensitive *Streptococcus pneumoniae, Streptococcus pyogenes, Bordetella pertussis, Legionella pneumophila, Chlamydia pneumoniae, Chlamydia trachomatis* in newborn infants of infected mothers, *Listeria monocytogenes, Mycoplasma pneumoniae*. *In-vitro* activity against *Haemophilus influenzae* has to be demonstrated.

Gastro-intestinal infections

Caused by *Campylobacter jejuni.*

Skin and soft tissue infections

Caused by *Streptococcus pyogenes, Staphylococcus aureus.*

Most strains of *Staphylococcus aureus* are sensitive to ERYKO-250 but resistance is increasing and may extend to other members of the macrolide group. Resistance may develop on treatment with an initially sensitive organism. ERYKO-250 has been used to treat acne vulgaris and actinomycosis.

Genitourinary infections

Caused by *Chlamydia trachomatis, Haemophilus ducreyi, Lymphogranuloma venereum, Ureaplasma urealyticum, Treponema pallidum, Neisseria gonorrhoeae.*

ERYKO-250 is not considered first line treatment for infections caused by *Neisseria gonorrhoeae* and *Treponema pallidum* (primary, secondary, early latent stage). Use of ERYKO-250 in pregnancy for treatment of *Treponema pallidum* may not prevent congenital syphilis.

Other

Relapsing fever due to *Borrelia* species.

Lyme disease

Listeriosis

Second line treatment of infections caused by *Clostridium tetani, Clostridium perfringens.*

Some atypical mycobacteria (*M. scrofulaceum, M. kansasii, M. avium-intracellulare).*

4.2 Posology and method of administration

Posology

Mild to moderate infection with susceptible organisms

Adults (oral): 500 mg (base) 8 hourly or 250 mg (base) 6 hourly.

For more severe infections, or those caused by less susceptible organisms, 1000 mg (base) three times daily and for unusually severe infections, 1000 mg (base) four times daily can be used.

Treatment should be continued for 48 hours or more after symptoms have resolved and temperature has returned to normal.

For the treatment of streptococcal pharyngitis, dosages should be continued for 10 days to prevent rheumatic fever or streptococcal glomerulonephritis.

Children (oral): 7,5 to 12,5 mg (base) / kg body weight every six hours or 15 to 25 mg/kg every 12 hours.

Syphilis

Adults (oral): In penicillin sensitivity, ERYKO-250 can be used as alternative for the treatment of early syphilis (primary, secondary, or early latent – less than one year) in a cumulative dose of 30 to 40 grams given in divided doses for a period of 15 to 20 days. For treatment of late syphilis (late latent and tertiary), 2 grams in divided doses for 30 days is recommended, but patients need to be closely followed up by serology as erythromycin has not been adequately evaluated in these cases. In the case of neurosyphilis, serial lumbar punctures to monitor efficacy of treatment are recommended.

Legionnaire's Disease

Adults (oral): 1 to 4 grams daily in divided doses.

Special populations

Elderly population

No special dosage recommendations.

Renal impairment

In case of severe kidney failure (creatinine clearance < 10 mL/min) and/or liver failure, reduce the dose and monitor closely (see section 4.4).

Hepatic impairment

Erythromycin is contraindicated in the case of severe hepatic insufficiency (see sections 4.3 and 4.4).

Paediatric population

Note: for younger children, infants and babies, erythromycin suspensions, are normally recommended.

Method of administration

ERYKO-250 is for oral use.

Optimal serum levels of ERYKO-250 are achieved when given immediately before meals.

4.3 Contraindications

ERYKO-250 is contraindicated in:

- Hypersensitivity to erythromycin or to any of the excipients listed in section 6.1.
- Hypersensitivity to other macrolides
- In case of severe hepatic insufficiency (see section 4.4)
- Concomitant administration with terfenadine,
  astemizole, cisapride, pimozide, ergotamine, dihydroergotamine,
  mizolastine, buspirone, carbamazepine, cyclosporin, colchicine, ebastine, halofantrine,
  lumefantrine, tacrolimus, theophylline, tolterodine and triazolam (see section 4.5).
- Erythromycin should not be used concomitantly with HMG-CoA reductase inhibitors (lovastatin or simvastatin) that are extensively metabolised by CYP3A4, due to the increased risk of myopathy, including rhabdomyolysis (see section 4.5 and 4.8).
- Concomitant intake of medicines, which can also lead to a prolongation of the QT interval, e.g. class IA and III antiarrhythmics, certain neuroleptics, tri- and tetracyclic antidepressants, arsenic trioxide, methadone, budipine, certain fluoroquinolones, imidazole-antimycotics, anti-malaria medicines, domperidone. Erythromycin may block the metabolism of disopyramide and thereby prolong the QT interval (see section 4.5).
- Disturbances of the electrolyte balance, especially in the case of hypokalaemia and hypomagnesaemia (see section 4.4).
- Clinically significant cardiac arrhythmia e.g. ventricular arrhythmia or in severe congestive heart failure (see section 4.4).
- Pregnancy and lactation (see section 4.6).
- Porphyria

4.4 Special warnings and precautions for use

As with other macrolides, rare serious allergic reactions, including acute generalised exanthematous pustulosis (AGEP) have been reported. If an allergic reaction occurs, ERYKO-250 should be discontinued and appropriate therapy should be instituted. Healthcare practitioners should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Severe, life-threatening allergic reactions may occur, e.g. severe skin reactions, such as erythema exudative multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis (especially in children of all ages) as well as angioneurotic oedema or anaphylaxis. At first signs of hypersensitivity reactions the treatment with erythromycin should be withdrawn immediately and the necessary emergency measures initiated in accordance with the presenting symptoms (see section 4.8).

Erythromycin is excreted principally by the liver, so caution should be exercised in administering the antibiotic to patients with impaired hepatic function or concomitantly receiving potentially hepatotoxic medicines.
Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur. There have been reports of transient hepatic dysfunction, including increased liver enzymes and hepatocellular and/or cholestatic hepatitis with or without jaundice, in patients receiving erythromycin (see sections 4.5 and 4.8).

Erythromycin is contraindicated in the case of severe hepatic insufficiency. A longer lasting therapy (2 to 3 weeks) with erythromycin can due to sensitisation lead to intrahepatic cholestasis and to cholestatic icterus partly with colicky abdominal pain, nausea, vomiting, urticaria, eosinophilia and fever, especially in already existing liver damage, in the case of repeated treatment and in allergies (see section 4.8). These reactions can occur even after initial application. The danger of occurrence increases at repeated administration and a therapy longer lasting than 10 days.

In case of severe kidney failure (creatinine clearance < 10 mL/min) and/or liver failure, reduce the dose and monitor closely. If signs of ototoxicity or liver toxicity appear, stop administering the product immediately (see section 4.8).

Cardiovascular events

Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in patients treated with macrolides including erythromycin (see sections 4.3, 4.5 and 4.8). Fatalities have been reported. Patients prescribed hydroxychloroquine or chloroquine concomitantly with erythromycin have a potentially increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

ERYKO-250 should be avoided in patients with a history of cardiac arrhythmias or a prolonged QT interval (see section 4.3). Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically significant bradycardia (< 50 bpm) coronary artery disease, history of ventricular tachycardia and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic medicines or potent CYP3A4 inhibitors (see section 4.3 and 4.5).

Elderly patients may be more susceptible to medicine-associated effects on the QT interval (see section 4.8).

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including erythromycin.

Pseudomembranous colitis has been reported with nearly all antibacterial medicines, including macrolides, and may range in severity from mild to life-threatening (see section. 4.8). Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial medicines including erythromycin and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial medicines 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 diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the use of antibacterial medicines.

Cross sensitivity with other macrolide antibiotics can exist, therefore in known hypersensitivity reactions against macrolides, special caution for use is recommended. Cross-resistance may occur between macrolide antibiotics themselves and the group of lincomycin.

The use of erythromycin in asthma patients being treated with theophylline requires particular vigilance regarding symptoms of intoxication by theophylline. The plasma levels of erythromycin should be monitored (see section 4.5).

Erythromycin is contraindicated during pregnancy and lactation (see section 4.3).
There have been reports suggesting erythromycin does not reach the foetus in adequate concentrations to prevent congenital syphilis. Infants born to women treated during pregnancy with oral erythromycin for early syphilis should be treated with an appropriate penicillin regimen.

There have been reports that erythromycin may aggravate the weakness of patients with myasthenia gravis.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with statins (see sections 4.3, 4.5 and 4.8).

There is a risk of developing visual impairments after exposure to erythromycin. For some patients, a pre-existing dysfunction in mitochondrial metabolism from genetic causes such as Leber's hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (ADOA) might play a contributing role (see section 4.8).

Estolate salt has been associated with increased incidence of hepatic dysfunction in pregnant women and should be avoided.
Erythromycin traverses the placental barrier; foetal plasma concentrations are about 5 to 20 % of those in the maternal plasma. As with any medication, care must be taken during pregnancy, especially the first trimester.

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. Reported epidemiological studies including data from meta-analyses suggest a 2-3-fold increase in the risk of IHPS following exposure to erythromycin in infancy. This risk is highest following exposure to erythromycin during the first 14 days of life. Available data suggests a risk of 2,6 % (95 % CI: 1,5 – 4,2 %) following exposure to erythromycin during this period. The risk of IHPS in the general population is 0,1-0,2 %. Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or chlamydia), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Parents should be informed to contact their doctor if vomiting or irritability with feeding occurs.

Pneumonia: due to the frequent resistance incidence of *Streptococcus pneumoniae* against macrolides; erythromycin should not be used as first-line therapy in the case of community acquired pneumonia. In the hospital acquired pneumonia, erythromycin should only be used in combination with other antibiotics.
In case of bacterial respiratory infections, uncomplicated skin and soft tissue infections and prophylaxis of rheumatic fever, treatment with erythromycin is only recommended when treatment with beta-lactam antibiotics or other suitable means is not possible.
The efficacy of other concomitantly taken medicines (such as oral contraceptives) may be impaired.

Laboratory tests: erythromycin interferes with the fluorometric determination of urinary catecholamines (see section 4.5).

Excipient: sodium

ERYKO-250 contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Excipient: lactose monohydrate

ERYKO-250 contains lactose monohydrate:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ERYKO-250.

4.5 Interaction with other medicines and other forms of interaction

Medicines that induce CYP3A4

Medicines such as rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort may induce the metabolism of erythromycin. This may lead to sub-therapeutic levels of erythromycin and a decreased effect. The induction decreases gradually during two weeks after discontinued treatment with CYP3A4 inducers. Erythromycin should not be used during and two weeks after treatment with CYP3A4 inducers.

Protease inhibitors

In concomitant administration of erythromycin and protease inhibitors, an inhibition of the decomposition of erythromycin has been observed.

Cimetidine

May inhibit the metabolism of erythromycin which may lead to an increased plasma concentration.

Xanthines

Xanthines (aminophylline, caffeine, theophylline) – serum concentrations may be increased. Dosage reduction of theophylline may need to be considered to prevent theophylline toxicity. Conversely, ERYKO-250 concentrations may be subtherapeutic when administered with theophylline.

Recent data from studies of erythromycin and its use in patients who are receiving high doses of theophylline reveal that the dose of theophylline should be reduced accordingly while the patient is receiving concomitant therapy with erythromycin. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant theophylline therapy.

Medicines metabolised by CYP450 system

Erythromycin is an inhibitor of cytochrome P450 isoenzymes, particularly CYP1A2 and CYP3A4 mediated metabolism and P-glycoprotein. The use of erythromycin in patients concurrently taking medicines metabolised by the cytochrome P450 system may be associated with elevations in serum levels of these medicines. Plasma concentrations of medicines metabolised by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin. The prescriber should consult appropriate reference sources for additional information. Particular care should be taken with medications known to prolong the QTc interval of the electrocardiogram. There have been reports of interactions of erythromycin with carbamazepine, ciclosporin, hexobarbital, phenytoin, alfentanil, disopyramide, bromocriptine, valproate, tacrolimus, quinidine, acenocoumarol, cilostazol, digoxin, methylprednisolone, omeprazole, rifabutin, vinblastine and antifungals e.g. fluconazole, ketoconazole and itraconazole.

Simvastatin, lovastatin and pravastatin

Concomitant use of HMG CoA Reductase inhibitors with erythromycin should be avoided due to significant inhibition of metabolism of HMG CoA Reductase inhibitors. Rare reports of rhabdomyolysis

have been reported in patients taking these medicines concomitantly. Caution is warranted if concurrent administration is deemed necessary (see section 4.3). Increased plasma concentration of pravastatin may be caused by erythromycin.

Contraceptives

Some antibiotics may in rare cases decrease the effect of contraceptive pills by interfering with the bacterial hydrolysis of steroid conjugates in the intestine and thereby reabsorption of unconjugated steroid. As a result of this plasma levels of active steroid may decrease.

Ergot Alkaloids

Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterised by severe peripheral vasospasm, hypertensive episodes, dysesthesia and ischaemia of the central nervous system, extremities and other tissues (see section 4.3).

Triazolobenzodiazepines (e.g., triazolam and alprazolam) and related benzodiazepines

Erythromycin has been reported to decrease the clearance of triazolam, midazolam and related benzodiazepines and thus may increase the pharmacological effect of these benzodiazepines.

Astemizole, terfenadine and mizolastine

ERYKO-250 significantly alters the metabolism of astemizole and terfenadine.

Care should be taken in the co-administration of erythromycin with H1 antagonists such as terfenadine, astemizole and mizolastine.

Erythromycin significantly alters the metabolism of astemizole, terfenadine, and mizolastine when taken concomitantly. Rare cases of serious, potentially fatal, cardiovascular adverse events including death, cardiac arrest, torsade de pointes and other ventricular arrhythmias

have been observed (see sections 4.3 and 4.4).

Mizolastine has a weak potential to prolong QT interval and has not been associated with arrhythmias, however as the metabolism of mizolastine is inhibited by erythromycin, therefore concomitant use should be avoided.

Anti-bacterial medicines

An *in vitro* antagonism exists between erythromycin and the bactericidal beta-lactam antibiotics (e.g., penicillin, cephalosporin). Erythromycin antagonises the action of clindamycin, lincomycin and chloramphenicol. The same applies for streptomycin, tetracyclines and colistin.

Cisapride and pimozide

Elevated cisapride levels have been reported in patients receiving erythromycin and cisapride concomitantly. This may result in QTc prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsade de pointes. Similar effects have been observed with concomitant administration of pimozide and another macrolide antibiotic – clarithromycin.

Colchicine

There have been post-marketing reports of colchicine toxicity with concomitant use of erythromycin and colchicine.

Verapamil

Hypotension, bradydysrhythmias and hyperlactataemia/lactic acidosis have been observed in patients receiving concurrent verapamil, a calcium channel blocker.

Zopiclone

Erythromycin has been reported to decrease the clearance of zopiclone and thus may increase the pharmacodynamic effects of this medicine.

Zolpidem

Slight increase in the sedative effects of zolpidem.

Anticoagulants

Excessive prolongation of prothrombin times/International Normalised Ratio (INR) in patients receiving erythromycin concurrently with chronic coumarin-type anticoagulant (e.g. warfarin) therapy has been reported. Such patients, particularly the elderly who generally exhibit slower coumarin-type anticoagulant clearance, may develop bleeding due to this interaction. In patients receiving erythromycin during chronic treatment with a coumarin-type anti-coagulant dosage should be adjusted accordingly.

Buspirone

Increased plasma concentrations of the anxiolytic medicine due to a decrease in its hepatic metabolism.

Disopyramide

Increased risk of the undesirable effects of disopyramide: severe hypoglycaemia, prolonged QT interval and serious ventricular arrhythmias, particularly torsades de pointes.

Ebastine

Increased risk of ventricular rhythm disorders in susceptible subjects (congenital long QT syndrome).

Halofantrine and lumefantrine

Increased risk of ventricular rhythm disorders, especially torsades de pointes. If possible, discontinue the macrolide. If the combination cannot be avoided, prior QT interval test and ECG monitoring should be done.

Digoxin

ERYKO-250 may increase digoxin serum concentrations. Monitoring of digoxin serum concentration is recommended.

Tolterodine

Should not be used concomitantly with erythromycin (see section 4.3).

Darifenacin

Increased concentrations of darifenacin, with the risk of increasing its undesirable effects. Clinical monitoring and possible adjustment of the dose of darifenacin.

Phosphodiesterase type 5 inhibitor (e.g., sildenafil, vardenafil)

Increased plasma concentrations of the PDE5 inhibitor, with risk of low blood pressure. Start treatment with the PDE5 inhibitor at the lowest dose when combined with one of these medicines.

Tyrosine-kinase inhibitors

Risk of increased undesirable effects of the tyrosine-kinase inhibitor due to a decrease in its metabolism. Clinical monitoring should be done.

Fexofenadine

Concomitant administration of erythromycin and fexofenadine result in 2- to 3-fold increase in plasma concentrations of fexofenadine, probably due to increased absorption.

Cyclosporin

The nephrotoxic effect of cyclosporin is enhanced by concomitant administration of erythromycin.

Corticosteroids

Erythromycin potentiates the effects of corticosteroids.

Domperidone

Concomitant use of domperidone and erythromycin is contraindicated due to its QT prolonging effect (see section 4.3).

Clozapine

Erythromycin can also interact with clozapine.

Cross-resistance

The development of resistance to erythromycin can appear rapidly and is usually associated with a cross-resistance with other macrolides (see section 4.5).

Urinary catecholamines

ERYKO-250 may cause falsely elevated concentrations of these medicines due to interference with the assay (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

ERYKO-250 traverses the placental barrier with concentrations in foetal plasma of 5 to 20 % of those found in maternal plasma.

There are no adequate and well-controlled studies in pregnant women. Observational studies in humans have reported cardiovascular malformations after exposure to medicines containing erythromycin during early pregnancy. There is a possible risk of cleft lips and palate in new-borns of mothers who have taken erythromycin.

ERYKO-250 for the treatment of syphilis in pregnant women may not penetrate the foetal circulation in quantities sufficient to prevent congenital syphilis. Infants born to these women should be treated with an appropriate penicillin regimen.

ERYKO-250 is not recommended for use during pregnancy (see section 4.3).

Breastfeeding

ERYKO-250 is distributed into breast milk.

There has been a report of a breast-fed infant who developed pyloric stenosis thought to be associated with the use of erythromycin by the mother. Erythromycin is concentrated in human breast milk and adverse effects have been seen in breast-fed infants whose mothers were receiving erythromycin. A cohort study concluded that the use of macrolides during breast feeding increased the risk of infantile hypertrophic pyloric stenosis.

Fertility

There are not sufficient data available to report on fertility.

4.7 Effects on ability to drive and use machines

Since adverse reactions such as nervous system disorders: dizziness, headache, somnolence, and eye disorders: visual impairments have been reported in patients receiving ERYKO-250, patients should not drive, use machinery or perform any tasks that require concentration,

until they are certain that ERYKO-250 does not adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post-market spontaneous reports with erythromycin.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**

Infections and infestations			Resistant bacteria or fungi caused superinfection. Pseudomembranous colitis
Blood and lymphatic system disorders		Agranulocytosis	Eosinophilia
Immune system disorders		Anaphylaxis	Urticaria, hypersensitivity
Metabolism and nutrition disorders			Decreased appetite
Psychiatric disorders			Hallucination, nightmares, psychoses and confusional state
Nervous system disorders		Seizures, and a myasthenia-like syndrome may occur.	Dizziness, headache, somnolence
Eye disorders			Visual impairment

Ear and labyrinth disorders		Reversible hearing loss at high doses (> 4 g per day)	Tinnitus and vertigo, reversible deafness
Cardiac disorders		Potentially life-threatening ventricular arrhythmias (ventricular tachycardia, torsades de pointes) (see section 4.3 and 4.4.)	
Vascular disorders			Hypotension thrombophlebitis and phlebitis
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal cramping or discomfort	Oral candidiasis, pancreatitis, pseudomembranous colitis	Infantile hypertrophic pyloric stenosis
Hepatobiliary disorders		Hepatotoxicity, may be a hypersensitivity reaction (more common with the estolate salt). Most cases are reversible with discontinuation of medication. Hepatitis,	Hepatomegaly and hepatic failure, hepatitis, hepatic dysfunction, cholestatic hepatitis with or without jaundice,

		abnormal liver function tests.	hepatocellular hepatitis
Skin and subcutaneous tissue disorders		Mild rashes, pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis	Rash and angioedema, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders		Myasthenia gravis	
Renal and urinary disorders		Vaginal candidiasis	Tubulointerstitial nephritis
Investigations			Liver function test abnormal, hepatic enzymes increased and electrocardiogram QT prolonged

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. Healthcare professionals 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

Signs and symptoms

Nausea, vomiting, diarrhoea, drowsiness.

Treatment

Treatment is symptomatic and supportive. Anaphylactic reactions should be treated with adrenaline, corticosteroids, antihistamines and vasopressors if indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Macrolides, ATC Code: J01FA01

Erythromycin belongs to the macrolide group of antimicrobials. It is produced by a strain of *Streptomyces erythraeus*.

Mechanism of action

Erythromycin may be either bacteriostatic or bactericidal, depending upon its serum concentration and the susceptibility of the micro-organism. *In-vivo* studies with susceptible organisms have shown that by increasing the dose from 1000 mg to 1500 mg daily, erythromycin is bactericidal. Erythromycin penetrates the bacterial cell membrane, reversibly binding to the 50S subunit of bacterial ribosomes, ultimately inhibiting protein synthesis within the cell. It is only effective against actively dividing cells and does not affect nucleic acid synthesis. Erythromycin concentrates within phagocytes and has intracellular bioactivity, hence its spectrum of activity against intracellular pathogens such as *Legionella pneumophila, Staphylococcus aureus* and *Listeria monocytogenes.*

5.2 Pharmacokinetic properties

Absorption

Bioavailability varies from 30 to 65 %, depending on the salt.

Distribution

After absorption, erythromycin diffuses readily into most body fluids, including middle ear and prostatic fluid, but the highest concentrations are in the liver, bile and spleen. Penetration of cerebrospinal fluid is poor, but may be enhanced with meningeal inflammation. Erythromycin may accumulate in patients with hepatic dysfunction. Erythromycin crosses the placenta, but concentrations in foetal plasma are low.

Biotransformation

It is highly plasma protein bound (70 to 90 %), with more than 90 % of the medicine metabolised in the liver and excreted in the bile.

Elimination

After oral administration, 2 to 5 % is excreted renally. The elimination half-life is 1,4 to 2 hours with normal renal function and 5 hours if anuric.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Maize starch,

calcium hydrogen phosphate,

sodium starch glycollate (Type A),

sodium citrate,

povidone (PVP K-30),

magnesium stearate,

purified talc,

magnesium hydroxide,

polacrillin potassium (Indion 294)

Tablet coating

Hydroxypropylmethylcellulose,

propylene glycol,

purifies talc

titanium dioxide (CI No. 77891),

erythrosine lake (CI No. 45430)

6.2 Incompatibilities

No known incompatibility.

6.3 Shelf life

Shelf life of 24 months in blister pack and Patient Ready Packs (PRP) packaging.

Shelf life of 48 months in HDPE container.

6.4 Special precautions for storage

Store in a cool, dry place at or below 25 °C.

Keep out of direct sunlight.

Do not remove the blister pack from the carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN

6.5 Nature and contents of container

Cartons containing 10 blister packs (composed of colourless PVC and silver coloured aluminium foil) of 10 tablets each. i.e. 100 tablets, or 2 x 10's i.e. 20 tablets, or 7 x 8's i.e. 56 tablets.

White polyethylene polymer plastic Patient Ready Packs containing 20, 40 or 56 tablets.

Colourless, transparent polypropylene polymer plastic packs packed in opaque white HDPE containers containing 100 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Shanur Healthcare (Pty) Ltd

Loch House Unit 003

3A Eton Road, Parktown

Johannesburg, 2193

Tel: +27 87 405 9660

8. REGISTRATION NUMBER

36/20.1.1/0222

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 23 September 2005

10. DATE OF REVISION OF THE TEXT

Date of last revision: