

NEW ZEALAND DATA SHEET

1. ERA Filmtabs (250 mg and 500 mg tablets)

ERA Filmtabs 250 mg and 500 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ERA Filmtabs 250 mg: Each tablet contains 250 mg erythromycin (as stearate).

ERA Filmtabs 500 mg: Each tablet contains 500 mg erythromycin (as stearate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White, ovaloid-shaped, film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ERA Filmtabs are indicated for the treatment of the following infections:

Streptococcus pyogenes: (Group A beta-haemolytic streptococcus) upper and lower respiratory tract, skin and soft tissue infections of mild to moderate severity.

Streptococcal pharyngitis and long term prophylaxis: although injectable benzathine penicillin G is considered by many as the drug of choice, erythromycin is an alternative when oral medication is preferred for treatment of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever, erythromycin is an alternate drug of choice.

When oral medication is given, the importance of strict adherence by the patient to the prescribed dosage regimen must be stressed. A therapeutic dose should be administered for at least 10 days.

Alpha-haemolytic streptococci (viridans group): although no controlled clinical efficacy trials have been conducted, oral erythromycin has been suggested for use in a regimen for prophylaxis against bacterial endocarditis in patients hypersensitive to penicillin who have congenital heart disease, or rheumatic or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the upper respiratory tract. Erythromycin is not suitable prior to genitourinary or gastrointestinal tract surgery.

Staphylococcus aureus: acute infections of skin and soft tissue of mild to moderate severity. Resistant organisms may emerge during treatment.

Streptococcus pneumoniae (Diplococcus pneumoniae): upper respiratory tract infections (e.g. otitis media, pharyngitis) and lower respiratory tract infections (e.g. pneumonia) of mild to moderate degree.

Mycoplasma pneumoniae (Eaton agent, PPLO): for respiratory infections due to this organism.

Haemophilus influenzae: for upper respiratory tract infections of mild to moderate severity. Not all strains of this organism are susceptible to erythromycin at concentrations achieved with usual therapeutic doses; resistant strains may require treatment with an advanced generation macrolide or other suitable antibiotics.

Chlamydia trachomatis: erythromycin is indicated for treatment of the following infections caused by Chlamydia trachomatis, conjunctivitis of the newborn, pneumonia of infancy and urogenital infections during pregnancy.

When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of uncomplicated urethral, endocervical or rectal infections in adults due to Chlamydia trachomatis.

Treponema pallidum: erythromycin is an alternate choice of treatment for primary syphilis in patients allergic to the penicillins. In the treatment of primary syphilis, spinal fluid examinations should be done before treatment and as part of follow-up after therapy.

Corynebacterium diphtheriae: as an adjunct to antitoxin, to prevent establishment of carriers, and to eradicate the organism in carriers.

Corynebacterium minutissimum: for the treatment of erythrasma.

Entamoeba histolytica: in the treatment of intestinal amoebiasis only. Extra-enteric amoebiasis requires treatment with other agents.

Listeria monocytogenes: infections due to this organism.

Neisseria gonorrhoeae: Erythromycin for injection in conjunction with erythromycin stearate orally, as an alternative drug in treatment of acute pelvic inflammatory disease caused by N. gonorrhoeae in female patients with a history of sensitivity to penicillin. Before treatment of gonorrhoea, patients who are suspected of also having syphilis should have a microscopic examination for T. pallidum (by immunofluorescence or darkfield) before receiving erythromycin, and monthly serologic tests for a minimum of 4 months.

Bordetella pertussis: erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Legionnaire's Disease: although no controlled clinical efficacy studies have been conducted, in vitro and limited preliminary clinical data suggest erythromycin may be effective in treating Legionnaire's Disease.

4.2 Dose and method of administration

Optimal serum levels of erythromycin are reached when ERA (erythromycin stearate) is taken in the fasting state or immediately before meals.

Method of administration

Oral

Dose

Adults:

The usual dosage range is from 250 mg every 6 hours or 500 mg every 12 hours, taken in the fasting state or immediately before meals. The total daily dose may be taken in two divided doses, once every 12 hours. Up to 4 g per day may be administered, depending upon the severity of the infection.

Paediatric population (children <12 years):

Age, weight and severity of the infection are important factors in determining the proper dosage. For the treatment of mild to moderate infections, the usual dosage is 30 to 50 mg/kg/day in 3 or 4 divided doses. When dosage is desired on a twice-a-day schedule, one-half of the total daily dose may be given every 12 hours in the fasting state or immediately before meals. For the treatment of more severe infections the total daily dose may be doubled.

A more suitable dosage form for children under 12 years might be erythromycin ethylsuccinate suspension.

For treatment of streptococcal infections: a therapeutic dosage of erythromycin should be administered for at least 10 days. In continuous prophylaxis of streptococcal infections in persons with a history of rheumatic heart disease, the dose is 250 mg twice a day.

For prophylaxis against bacterial endocarditis in patients allergic to penicillin with congenital heart disease, or rheumatic or other acquired valvular heart disease when undergoing dental procedures or surgical procedures of the upper respiratory tract: 1 g (20 mg/kg for children) orally 1.5 to 2 hours before the procedure, and then 500 mg (10 mg/kg for children) orally every 6 hours for 8 doses.

For conjunctivitis of the newborn caused by Chlamydia trachomatis: oral erythromycin suspension 50 mg/kg/day in 4 divided doses for at least 2 weeks.

For pneumonia of infancy caused by Chlamydia trachomatis: although the optimal duration of therapy has not been established, the recommended therapy is oral erythromycin suspension 50 mg/kg/day in 4 divided doses for at least 3 weeks.

For urogenital infections during pregnancy due to Chlamydia trachomatis: although the optimal dose and duration of therapy have not been established the suggested treatment is erythromycin 500 mg, by mouth, 4 times a day on an empty stomach for at least 7 days. For women who cannot tolerate this regimen, a decreased dose of 250 mg, by mouth, 4 times a day should be used for at least 14 days.

For adults with uncomplicated urethral, endocervical, or rectal infections caused by Chlamydia trachomatis in whom tetracyclines are contraindicated or not tolerated: 500 mg, by mouth, 4 times a day for at least 7 days.

For treatment of primary syphilis: 30 to 40 g given in divided doses over a period of 10 to 15 days.

For treatment of acute pelvic inflammatory disease caused by N. gonorrhoeae: 500 mg erythromycin for injection every 6 hours for 3 days, followed by 250 mg ERA orally every 6 hours for 7 days.

For intestinal amoebiasis:

Adults: 250 mg four times daily for 10 to 14 days.

Children: 30 to 50 mg/kg/day in divided doses for 10 to 14 days.

For use in pertussis: although optimal dosage and duration have not been established, doses of erythromycin utilised in reported clinical studies were 40 to 50 mg/kg/day, given in divided doses for 5 to 14 days.

For treatment of Legionnaire's Disease: although optimal doses have not been established, doses utilised in reported clinical data were 1 to 4g daily in divided doses.

4.3 Contraindications

ERA is contraindicated in patients with known hypersensitivity to erythromycin, or to any of the excipients listed in section 6.1.

Severely impaired hepatic function.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, cisapride, pimozide, and ergotamine or dihydroergotamine. (See section 4.5)

Erythromycin should not be given to patients with a history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (see section 4.4 and 4.5)

Erythromycin should not be given to patients with electrolyte disturbances (hypokalaemia, hypomagnesaemia due to the risk of prolongation of QT interval).

4.4 Special warnings and precautions for use

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.

Erythromycin should be used with caution in the following:

Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia.

Patients concomitantly taking other medicinal products associated with QT prolongation (see section 4.3 and 4.5)

Elderly patients may be more susceptible to drug- 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. Consideration of these findings should be balanced with treatment benefits when prescribing erythromycin.

Hepatic dysfunction including increased liver enzymes and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with erythromycin.

As erythromycin is principally excreted by the liver, caution should be exercised when administering erythromycin to patients with impaired liver function.

There have been reports suggesting erythromycin does not reach the foetus in adequate concentration 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.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life threatening.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin.

Prolonged or repeated use of erythromycin may result in an overgrowth of non-susceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued, and appropriate therapy instituted.

When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy.

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

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. 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 time 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 physician if vomiting or irritability with feeding occurs.

Increased INR levels have been reported in patients when macrolide and coumarin anticoagulants are used concomitantly. Patients using macrolide and coumarin anticoagulants should be closely monitored (see section 4.5).

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

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

Paediatric population:

In young children the use of magnesium hydroxide can produce a hypermagnesemia, especially if they present renal impairment or dehydration.

4.5 Interaction with other medicines and other forms of interaction

QT prolongation medicines

There is a rare risk of serious cardiovascular adverse events, including QT interval prolongation, cardiac arrest, torsades de pointes and cardiac arrhythmias, with erythromycin alone and with the concomitant administration of erythromycin with other medicines that prolong the QT interval.

Examples of medicines that prolong the QT interval include class IA and III antiarrhythmics (e.g. amiodarone), antipsychotics (e.g. risperidone, haloperidol), antidepressants (e.g. citalopram) and fluoroquinolones (e.g. ciprofloxacin) (see section 4.4).

Erythromycin use in patients who are receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

There have been published reports suggesting when oral erythromycin is given concurrently with theophylline there is a significant decrease in erythromycin serum concentrations. This decrease could result in sub-therapeutic concentrations of erythromycin.

Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin serum levels.

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants (e.g. warfarin, rivaroxaban) were used concomitantly.

Triazolobenzodiazepines (such as triazolam and alprazolam) and related benzodiazepines: Erythromycin has been reported to decrease the clearance of triazolam, and midazolam, and thus may increase the pharmacologic effect of these benzodiazepines.

The use of erythromycin in patients concurrently taking drugs metabolised by the cytochrome P450 system may be associated with elevations in serum levels of these drugs. There have been reports of interactions of erythromycin with carbamazepine, cyclosporine, hexobarbital, phenytoin, alfentanil, disopyramide, bromocriptine, valproate, tacrolimus, quinidine, methylprednisolone, cilostazol, vinblastine, sildenafil, terfenadine, astemizole, and rifabutin. Serum concentrations of drugs metabolised by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin.

Erythromycin significantly alters the metabolism of astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events including cardiac arrest, torsade de pointes and other ventricular arrhythmias have been observed. (See sections 4.3 and 4.8).

Erythromycin significantly alters the metabolism of terfenadine when taken concomitantly. Rare cases of serious cardiovascular adverse events including death, cardiac arrest, torsades de pointes and other ventricular arrhythmias have been observed (see sections 4.3 and 4.8).

Elevated cisapride levels have been reported in patients receiving erythromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsade de pointes (see sections 4.3 and 4.8). Similar effects have been observed in patients taking pimozide and clarithromycin, another macrolide antibiotic.

Erythromycin has been reported to decrease the clearance of zopiclone and thus may increase the

pharmacodynamic effects of this drug.

HMG-CoA Reductase Inhibitors: Erythromycin has been reported to increase concentrations of HMG-CoA Reductase inhibitors (e.g. lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

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

Post-marketing reports indicate that co-administration of erythromycin 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. (See section 4.3).

Urine alkalisation secondary to administration of magnesium hydroxide may modify excretion of some drugs; thus, increased excretion of salicylates has been seen.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats dosed by oral gavage at 350 mg/kg/day (7 times the human dose) of erythromycin base prior to and during mating, during gestation, and through weaning.

No evidence of teratogenicity or embryotoxicity was observed when erythromycin base was given by oral gavage to pregnant rats and mice at 700 mg/kg/day (14 times the human dose), and to pregnant rabbits at 125 mg/kg/day (2.5 times the human dose).

A slight reduction in birth weights was noted when female rats were treated prior to mating, during mating, gestation and lactation at a high oral dosage of 700 mg/kg/day of erythromycin base; weights of the offspring were comparable to those of the controls by weaning. No evidence of teratogenicity or effects on reproduction was noted at this dosage. When administered during late gestation and lactation periods, this dosage of 700 mg/kg/day (14 times the human dose) did not result in any adverse effects on birth weight, growth and survival of offspring.

There are no adequate and well controlled studies in pregnant women. However, observational studies in humans have reported cardiovascular malformations after exposure to medicinal products containing erythromycin during early pregnancy.

Erythromycin has been reported to cross the placental barrier in humans, but foetal plasma levels are generally low.

Erythromycin should be used by women during pregnancy only if clearly needed.

The effect of erythromycin on labour and delivery is unknown.

Breast-feeding

Erythromycin appears in breast milk. It is not known whether it can harm the nursing child. The expected benefits and the potential hazards should be carefully assessed.

Fertility

There was no apparent effect on male or female fertility in rats treated with erythromycin base by oral gavage at 700 mg/kg/day.

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

The undesirable effects are presented below using the following frequency categories.

Very rare: may affect up to 1 in 10,000 people

Not known: frequency cannot be estimated from the available data

The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose related. They include nausea, vomiting, diarrhoea and anorexia.

Gastrointestinal disorders

Not known: Abdominal pain

Metabolism and nutrition disorders

Very rare: Hypermagnesemia. Observed after prolonged administration of magnesium hydroxide to patients with renal impairment.

Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur (see section 4.4).

Pseudomembranous colitis has been rarely reported in association with erythromycin therapy.

There have been isolated reports of transient central nervous system side effects including confusion, hallucinations, seizures, vertigo, and tinnitus; however, a cause and effect relationship has not been established.

Erythromycin has been associated with the production of potentially life-threatening ventricular arrhythmias, including ventricular tachycardia and torsades de pointes, in individuals with prolonged QT interval (see section 4.4).

Cardiac disorders

Cardiac arrest, ventricular fibrillation (frequency not known)

Skin and subcutaneous tissue disorders

Not known: Acute generalized exanthematous pustulosis (AGEP)

Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred. Skin reactions ranging from mild eruptions to erythema multiforme, Stevens- Johnson syndrome and toxic epidermal necrolysis have rarely been reported.

There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

There have been rare reports of pancreatitis and convulsions.

There have been reports of interstitial nephritis coincident with erythromycin use.

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 <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Reports indicate that the ingestion of large amounts of erythromycin can be expected to produce gastrointestinal distress, hearing problems and other adverse effects (see section 4.8). Allergic reactions and accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. Erythromycin serum levels are not appreciably altered by haemodialysis or peritoneal dialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Macrolides, ATC code: J01FA01.

Erythromycin, a member of the macrolide class of antibiotics, is active against a number of gram-positive and some-gram negative organisms. These include:

- Streptococcus pyogenes
- Streptococcus viridans
- Streptococcus pneumoniae
- Staphylococcus aureus
- Clostridia
- Corynebacterium

- Neisseria
- Haemophilus
- Bordetella

It is also active against *Mycoplasma pneumoniae*, *Ureaplasma urealyticum*, *Chlamydia trachomatis*, *Campylobacter fetus* subspecies *jejuni*, the causative organism of Legionnaire's Disease and *Treponema pallidum*.

Not all strains of the organism listed above are sensitive and culture and susceptibility testing should be done.

Disc Susceptibility Tests

Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One recommended procedure uses erythromycin class discs for testing susceptibility; interpretations correlate zone diameters of this disc test with MIC values for erythromycin. With this procedure, a report from the laboratory of "susceptible" indicates the infecting organism is likely to respond to therapy. A report of "resistant" indicates the infective organism is not likely to respond to therapy. A report of intermediate susceptibility indicates the result be considered equivocal, and, if the pathogen is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation.

Note: many strains of *Haemophilus influenzae* are resistant to erythromycin alone, but are susceptible to erythromycin and sulphonamides together. Staphylococci resistant to erythromycin may emerge during a course of erythromycin therapy. Culture to susceptibility testing should be performed.

Biochemical tests demonstrate erythromycin inhibits protein synthesis of the pathogen without directly affecting nucleic acid synthesis. Antagonism has been demonstrated between clindamycin, lincomycin and chloramphenicol and erythromycin.

Erythromycin binds to the 50S ribosomal subunits of susceptible bacteria and suppresses protein synthesis.

5.2 Pharmacokinetic properties

Orally administered erythromycin stearate is readily and reliably absorbed. Optimal serum levels of erythromycin are reached when it is taken in the fasting state or immediately before meals.

Erythromycin diffuses readily into most body fluids. Only low concentrations are normally achieved in the spinal fluid but passage of erythromycin across the blood-brain barrier increases in meningitis.

In the presence of normal hepatic function, erythromycin is concentrated in the liver and excreted in the bile; the effect of hepatic dysfunction on excretion of erythromycin by the liver into the bile is not known.

In patients with liver disease the half-life has been shown to be significantly increased but this is of little clinical significance.

Less than 5% of the orally administered dose of erythromycin is excreted in active form in the urine.

5.3 Preclinical safety data

Carcinogenesis

Long term (2 year) oral studies conducted in rats up to 400 mg/kg/day and in mice up to about 500 mg/kg/day with erythromycin stearate did not provide evidence of tumorigenicity.

Mutagenesis

Mutagenicity studies conducted did not show any genotoxicity potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose

Macrogol 400

Macrogol 8000

Magnesium hydroxide

Maize starch

Polacrillin potassium

Povidone

Sorbic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

ERA Filmtabs (250 mg and 500 mg tablets) are supplied in plastic bottles, each containing 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

ERA Filmtabs 250 mg: 31 December 1969

ERA Filmtabs 500 mg: 3 March 1973

10. DATE OF REVISION OF THE TEXT

30 June 2021

Summary table of changes:

Section changed	Summary of new information
4.3, 4.4 and 4.8	Cardiovascular risk has been added
4.4	Addition of Risk of Infantile Hypertrophic Pyloric Stenosis (IHPS) in infants on exposure to Erythromycin
4.5	Addition of warfarin and rivaroxaban to drug interactions following concomitant use with Erythromycin