ERYTHRO TEVA

TABLETS.

Composition

Erythro Teva 250 mg Tablets
Each tablet contains:

Active Ingredient

Erythromycin (as stearate)	250 mg

Other Ingredients
Starch, povidone, docusate sodium, magnesium stearate, lactose, talc, eudragit E-30 D (ethyl acrylate/methyl acrylate polymer) titanium dioxide, polyethylene glycol 6000, carboxymethylcellulose sodium, simethicone.

Sodium content per tablet: 0.112 mg-0.134 mg.
Lactose content per tablet: 285.6 mg.

Erythro Teva 500 mg Tablets
Each tablet contains:

Active Ingredient

Erythromycin (as stearate)	500 mg

Other Ingredients
Magnesium hydroxide, sodium starch glycolate, povidone, polysorbate 80, magnesium stearate, lactose, hydroxypropylmethylcellulose, titanium dioxide, polydextrose, polyethylene glycol 4000.

Sodium content per tablet: 1.45 mg- 2.31mg.
Lactose content per tablet: 296.50 mg.

Mechanism of Action

Erythromycin is a highly effective antibacterial agent which acts by the inhibition of protein synthesis. It is readily absorbed from the gastrointestinal tract and, following absorption, it diffuses readily into most body fluids. Erythromycin is concentrated in the liver and excreted in the bile.

Erythromycin is virtually devoid of nephrotoxic, hepatotoxic, neurotoxic or photosensitivity reactions.

Erythromycin is active against the following microorganisms:

- Streptococcus pyogenes (group A β-hemolytic streptococcus)
- α-hemolytic streptococci (viridans group)
- Staphylococcus aureus
- Streptococcus pneumoniae (Diplococcus pneumoniae)
- Mycoplasma pneumoniae
- Haemophilus influenzae
- Treponema pallidum
- Corynebacterium diphtheriae
- Corynebacterium minutissimum
- Listeria monocytogenes
- Neisseria gonorrhoea
- Chlamydia trachomatis

• Nocardia
• Campylobacter jejuni
• Bordetella pertussis
• Legionella pneumophila
• Entameba histolytica
• Ureaplasma urealyticum.

Erythromycin is particularly active against Gram-positive organisms. Consequently, the problem of overgrowth of non-susceptible organisms is of very low incidence.

Erythro Teva is a suitable alternative to penicillins in the treatment and prophylaxis of infections due to Gram-positive cocci, especially streptococci, particularly in patients for whom penicillins are contraindicated.

Indications

Treatment of the following infections when caused by susceptible organisms:
• Upper and lower respiratory tract infections.
• Skin and soft tissue infections.
• Conjunctivitis of the newborn caused by Chlamydia trachomatis.
• Urogenital infections caused by Chlamydia trachomatis.
• Enteric infections caused by Campylobacter jejuni.
• Venereal diseases (as an alternative regimen to penicillins and tetracyclines).
• Intestinal amebiasis.
• Legionnaires' disease.
• Long-term prophylaxis in rheumatic fever.
• Short-term prophylaxis against bacterial endocarditis in patients hypersensitive to penicillin who have congenital heart disease, or rheumatic or other acquired valvular heart disease, when undergoing dental procedures and surgical procedures of the upper respiratory tract.

Contraindications

Known hypersensitivity to the drug, to other antibiotics from the macrolide family, or to any other ingredient of the preparation.

Concomitant administration with the following drugs:
Terfenadine, astemizole, mizolastine, cisapride, pimozide, sertindole, ergotamine or dihydroergotamine, simvastatin, tolterodine , amisulpride
(see Drug Interactions).

Severely impaired hepatic function

Warnings

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.

In patients with impaired hepatic function or in those taking concomitant potentially hepatotoxic agents, liver function should be monitored, since a few reports of hepatic dysfunction have been received in patients taking erythromycin as the estolate, base or stearate. Extended administration requires regular evaluation particularly of liver function. Therapy should be dicontinued if significant hepatic dysfunction occurs.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored for creatine kinase (CK) and serum transaminase levels (see also Drug Interactions).

Rhabdomyolysis has been reported with concomitant use of erythromycin and HMG-CoA reductase inhibitors.

Patients receiving erythromycin concurrently with drugs which can cause prolongation of the QT interval should be carefully monitored; the concomitant use of erythromycin with some of these drugs is contraindicated

Erythromycin may interfere with the determination of urinary catecholamines and 17-hydroxycorticosteroids levels.

There have been reports suggesting that erythromycin does not reach the fetus 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.

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

Genotoxicity
Erythromycin was not genotoxic in assays for bacterial and mammalian mutagenicity and for clastogenicity *in vitro*. The clastogenic potential of erythromycin has not been investigated *in vivo*.

Impairment of 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 (approximately 9 times the maximum human dose

Use in Pregnancy
There is no evidence of hazard from erythromycin in human pregnancy. It has been in widespread use for a number of years without apparent ill consequence. Animal studies have shown no hazard.

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

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Use in Breastfeeding
Erythromycin is excreted in breast milk, therefore, caution should be exercised when erythromycin is administered to nursing mothers.

Adverse Reactions

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

Blood and lymphatic system disorders:
Eosinophilia.

Cardiac disorders
QTc interval prolongation, torsades de pointes, palpitations, and cardiac rhythm disorders including ventricular tachyarrhythmias (manifested by chest pain).

Ear and labyrinth disorders
Deafness, tinnitus
There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency or high doses.

Gastrointestinal disorders
The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. The following have been reported:
upper abdominal discomfort, nausea, vomiting, diarrhoea, pancreatitis, anorexia, infantile hypertrophic pyloric stenosis.
Pseudomembranous colitis has been rarely reported in association with erythromycin therapy (see section 4.4).

General disorders and administration site conditions
Chest pain, fever, malaise.

Hepatobiliary disorders
Cholestatic hepatitis, jaundice, hepatic dysfunction/abnormal liver function test results, hepatomegaly, hepatic failure, hepatocellular hepatitis (see section 4.4).

Immune system disorders
Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred.

Investigations
Increased liver enzyme values.

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

Psychiatric disorders
Hallucinations

Renal and urinary disorders
Interstitial nephritis

Skin and subcutaneous tissue disorders
Skin eruptions, pruritus, urticaria, exanthema, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.

Vascular disorders
Hypotension.

Precautions

Since erythromycin is excreted principally by the liver, caution should be exercised in administering the antibiotic to patients with impaired hepatic function or concomitantly receiving hepatotoxic agents..

Liver function test should be performed when large doses of erythromycin are administered.

Prolonged or repeated use may result in overgrowth of non-susceptible bacteria or fungi. Use of this medication for prolonged or repeated periods may result in oral thrush or a new vaginal yeast infection (oral or vaginal fungal infection). The doctor should be informed if the following appears: white patches in the mouth, a change in vaginal discharge or other new symptoms. Should superinfection occur, the drug should be discontinued and/or appropriate therapy instituted.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including erythromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis". *Clostridium difficile* produces toxins A and B which contribute to the development of *Clostridium difficile* associated diarrhea (CDAD). Hypertoxin producing strains of *Clostridium difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. 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.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile colitis.*

There have been reports that 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. Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or neonatal Chlamydia trachomatis infections), 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.

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

In the treatment of streptococcal infections, a therapeutic dosage of erythromycin should be administered for at least 10 days.

Owing to the presence of lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine.

Drug Interactions

Note: Erythromycin, through inhibition of the 3A isoform subfamily of the cytochrome P 450 microsomal enzyme systems (CYP3A), can reduce the hepatic metabolism of some drugs that are metabolized through this pathway, thereby decreasing elimination and increasing serum concentrations of these drugs. Serum concentrations of drugs metabolized by cytochrome P 450 microsomal enzyme systems should therefore be monitored closely, and their dosage adjusted if necessary, in patients receiving erythromycin concomitantly.

Erythromycin/ Oral Anticoagulants: Concurrent use may increase the pharmacological effects of oral anticoagulants, requiring a lower dose of anticoagulant. Increased anticoagulation effects due to interactions of erythromycin with oral anticoagulants may be more pronounced in the elderly

Erythromycin/ Xanthines (e.g. Theophylline): Concurrent use may decrease theophylline hepatic clearance, resulting in increased serum theophylline levels and 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.

Erythromycin/ Penicillins: Since bacteriostatic drugs may interfere with the bactericidal effect of penicillins in the treatment of meningitis or other situations where a rapid bactericidal effect is necessary, it is best to avoid concurrent therapy.

Erythromycin/ Carbamazepine: Concurrent administration may increase serum levels of carbamazepine by inhibition of hepatic metabolism.

Erythromycin/ Digoxin: Concomitant administration of digoxin and erythromycin may produce elevated digoxin levels via increased bioavailability in a small subset of patients (<10%) who metabolize significant amounts of digoxin in the gut. Therapeutic and toxic effects of digoxin may be increased.

Erythromycin/ Lovastatin and other HMG-CoA Reductase Inhibitors: Rhabdomyolysis, with or without renal impairment, has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin or simvastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Erythromycin/ Sildenafil: Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. Reduction of sildenafil dosage should be considered.

Erythromycin/ Terfenadine: Concomitant administration may cause an increase in terfenadine plasma levels, due to the inhibition of terfenadine metabolism by erythromycin (or other macrolide antibiotics). High plasma concentrations of terfenadine have been reported to prolong the QT-interval and cause life-threatening cardiac arrhythmias. Therefore, such combination should be avoided (see Contraindications.)

Erythromycin/ Astemizole: Erythromycin is known to impair the cytochrome P450 enzyme system which also influences astemizole metabolism. There have been two reports to date of syncope with torsades de pointes, requiring hospitalization in patients taking combinations of astemizole 10 mg daily with erythromycin. In each case, the QT intervals were prolonged beyond 650 milliseconds at the time of the event. Therefore, concomitant administration of astemizole with erythromycin is contraindicated.

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

Erythromycin/Cisapride: Erythromycin is known to impair the cytochrome P450 enzyme system which also influences cisapride metabolism. This may lead to elevated plasma levels of cisapride. Prolongation of the QT-interval on the ECG has been reported as a result of elevated cisapride levels. Therefore, cisapride treatment should be discontinued in patients receiving erythromycin.

***Erythromycin/Pimozide**:* Concomitant administration of macrolide antibiotics, including erythromycin, may lead to an increase in pimozide serum levels through inhibition of cytochrome P450 microsomal enzyme system by erythromycin. Such alterations in the pharmacokinetics of pimozide may be associated with prolongation of the QT-interval, predisposing to serious cardiovascular effects, including ventricular arrhythmias. Also, the use of macrolide antibiotics in patients with prolonged QT-interval has been rarely associated with ventricular arrhythmias.
Two sudden deaths have been reported when clarithromycin was added to ongoing pimozide therapy. Therefore, such combinations are contraindicated (see Contraindications).
Erythromycin/ Disopyramide: Initiation of erythromycin therapy in several patients receiving disopyramide reportedly has been associated with elevated serum disopyramide concentrations, QT-interval prolongation, and polymorphic ventricular tachycardia.
Erythromycin/Ergotamine/Dihydroergotamine: Concurrent use of erythromycin with ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity, characterized by severe peripheral vasospasm and dysesthesia (see Contraindications).
Erythromycin/ Cyclosporine: Concomitant administration of erythromycin and cyclosporine has been reported to increase cyclosporine plasma concentrations and may increase the risk of nephrotoxicity.
Erythromycin/ Triazolbenzodiazepines (e.g., Midazolam/Triazolam), and Related Benzodiazepines: Concurrent administration of erythromycin with these agents has been reported to decrease their clearance, and thus increase the pharmacologic effects of these agents.
It is not known whether concomitant administration of erythromycin with other benzodiazepines results in similar alterations of pharmacokinetics of the benzodiazepines.
Erythromycin/Hexobarbital/Valproate/Phenytoin/ Bromocriptine/ Loratadine/ Alfentanil: Concurrent use may lead to increase in serum concentrations of these agents due to the inhibition of microsomal enzyme systems by erythromycin..
Erythromycin/ Chloramphenicol/ Lincomycins (including Clindamycin): Chloramphenicol or lincomycins may be displaced from or prevented from binding to 50S subunits of bacterial ribosomes by erythromycin, thus antagonizing the effects of chloramphenicol, lincomycins and clindamycin; thus concurrent use is not recommended.
Erythromycin/ Hepatotoxic Medications: Concomitant use of erythromycin with hepatotoxic medications may increase the potential for hepatotoxicity of these medications.
Erythromycin/ Protease Inhibitors: In concomitant administration of erythromycin and protease inhibitors, an inhibition of the decomposition of erythromycin has been observed.
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.
Erythromycin/Colchicine: There have been post-marketing reports of colchicine toxicity with concomitant use of erythromycin and colchicine.
Erythromycin/Verapamil: Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients receiving concurrent verapamil, a calcium channel blocker.
Erythromycin/Cimetidine: Cimetidine may inhibit the metabolism of erythromycin which may lead to an increased plasma concentration.
Erythromycin/Zopiclone: Erythromycin has been reported to decrease the clearance of zopiclone and thus may increase the pharmacodynamic effects of this drug

Other CYP3A Based Interactions with Erythromycin:

There have been spontaneous or published reports of CYP3A based interactions of erythromycin with tacrolimus, rifabutin, quinidine, methylprednisolone, cilostazol, and vinblastine.

Increase in the serum concentrations of the following drugs (metabolized by the cytochrome P450 enzyme system) may occur when erythromycin is administered concurrently with: omeprazole, antifungals, e.g.: fluconazole, ketoconazole, and intraconazole.

Drugs that induce CYP3A4 (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

Drugs Metabolized by the Cytochrome P450

The use of erythromycin in patients concurrently taking drugs metabolized 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 metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin. (see also Contraindications).

Other drugs metabolized by the cytochrome P450 system, such as acenocoumarol, atorvastatin, buspirone, cabergoline, clozapine, digoxin, eletriptan, felodipine, midazolam, quetiapine, tadalafil, theophylline, triazolam, warfarin and zopiclone, may be associated with elevated serum levels if administered concomitantly with erythromycin. Because of the risk of toxicity, appropriate monitoring should be undertaken, and dosage should be adjusted as necessary.

Diagnostic Interference

Erythromycin interferes with the fluorometric determination of urinary catecholamines, falsely elevating the concentrations of urinary catecholamines, 17-hydroxycorticosteroids, and 17-ketosteroids.

Erythromycin may interfere with colorimetric assays resulting in falsely increased AST (SGOT) and ALT (SGPT) concentrations. Falsely elevated AST concentrations without liver injury may result due to erroneous measurement of unidentified metabolites of erythromycin in colorimetiic determinations.

Erythromycin may decrease serum folate assay results if a microbiologic method is used, since the drug can inhibit the growth of *Lactobacillus casei*; results are unaffected if the chromatographic procedure of Landon is used.

The presence of erythromycin in the blood may interfere with the etiologic diagnosis of mycoplasmal pneumonia by masking a rise in the titer of the tetrazolium reduction inhibition neutralizing antibody to *Mycoplasma pneumoniae.*

Information for Patients

Patients should be counseled that antibacterial drugs including erythromycin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When erythromycin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by erythromycin or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Dosage and Administration

• Erythro Teva Tablets should be taken on an empty stomach.
• In the treatment of streptococcal infections, a therapeutic dosage should be administered for at least 10 days.

Treatment of Infections

The following is the usual recommended dosage. In more severe infections, dosage may be doubled.

All doses are expressed in terms of erythromycin base.

Adults: The usual adult dosage is 250 mg erythromycin (as stearate), every 6 hours. This may be increased up to 4 g/day according to severity of infection.

If a twice-daily dosage is desired, 1/2 of the total daily dose may be given every 12 hours. However, twice-daily dosage is not recommended when doses higher than 1 g daily are administered.

Doses may also be given 3 times daily by administering 1/3 of the total daily dose every 8 hours.

The following are dosage recommendations for specific indications:

Chlamydia Trachomatis Infections

Urogenital infections during pregnancy (see Warnings): 500 mg (as stearate), 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 (as stearate), 4 times a day should be used for at least 14 days.

Adults with Uncomplicated Urethral, Endocervical, or Rectal Infections Caused by Chlamydia Trachomatis, in Whom Tetracyclines Are Contraindicated or Not Tolerated: 500 mg (as stearate), 4 times a day for at least 7 days.

Legionnaires' Disease:

1-4 g/day (as stearate), in divided doses.

Intestinal Amebiasis:

The standard dosage should be administered for a period of 10-14 days.

Prophylaxis of Infections

Long-term Prophylaxis:

In continuous prophylaxis against recurrences of streptococcal infections in persons with a history of rheumatic heart disease, the usual dosage is 250 mg (as stearate), twice daily.

Short-term Prophylaxis:

For prophylaxis against bacterial endocarditis in patients 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 as stearate, administered orally, 1 1/2-2 hours before the procedure.
This should be followed by 500 mg as stearate administered orally every 6 hours for 8 doses.

Overdosage

Manifestations

In doses of over 2 g per day, abdominal discomfort, nausea, or diarrhea may occur.

Treatment

No specific treatment has been proposed. Treatment should be symptomatic and supportive. The patient should be monitored for signs of possible hepatotoxicity.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

Storage

Store in a dry place below 25°C.

Registration Numbers:

Erythro Teva 250 mg Tablets: 139.10.24747.00.
Erythro Teva 500 mg Tablets: 031 11 25658 03.

Manufacturer

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