Product Monograph

EES 600 Tablets 600 mg
(erythromycin ethylsuccinate tablets USP)

THERAPEUTIC CLASSIFICATION

Antibiotics

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(erythromycin ethylsuccinate tablets USP)

THERAPEUTIC CLASSIFICATION

Antibiotics

ACTION

Erythromycin exerts its antibacterial action by binding to the 50 S ribosomal subunit of susceptible bacteria and suppressing protein synthesis. Erythromycin is usually bacteriostatic but may be bactericidal in high concentrations or against highly susceptible organisms.

INDICATIONS AND CLINICAL USES

Erythromycin may be indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Upper respiratory tract infections of mild to moderate severity caused by *S.pyogenes* (group A beta-hemolytic streptococci), *S. pneumoniae* and *H. influenzae*. Not all strains of *H. influenzae* are susceptible to erythromycin at the concentrations of the antibiotic achieved with usual therapeutic doses.

Lower respiratory tract infections of mild to moderate severity caused by *S.pyogenes* (group A beta-hemolytic streptococci), *S. pneumoniae* and *M. pneumoniae.*

Skin and soft tissue infections of mild to moderate severity caused by *S. pyogenes* and *S. aureus* (resistance of staphylococci may emerge during treatment).

Primary syphilis caused by *T. pallidurn*. Erythromycin may be an alternate choice of treatment for primary syphilis in patients allergic to penicillins. Spinal fluid examinations should be performed before treatment and as part of the post-therapy follow-up.

Diphtheria caused by *C. diphtheriae*. As an adjunct to antitoxin, to prevent the establishment of carriers, and to eradicate the organisms in carriers.

Erythrasma caused by *C. minutissimum.*

Pertussis caused by *B. pertussis*. Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them non-infectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Legionnaires' disease caused by *L. pneumophila.* Although no controlled clinical efficacy studies have been conducted, in vitro and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' disease.

Specimens for bacteriologic culture should be obtained prior to therapy in order to isolate and identify the causative organisms and to determine their, susceptibility to erythromycin. Therapy may be instituted before results of susceptibility studies are known; however, antibiotic treatment should be re-evaluated when the results become available or if the clinical response is not adequate.

Chlamydial Infections: The 1988 "Canadian Guidelines for the Treatment of Sexually Transmitted Diseases in Neonates, Children, Adolescents and Adults" recommends erythromycin for the treatment of the following infections when caused by *Chlamydia trachomatis:*

1. In newborns and infants for conjunctivitis and pneumonia.
NOTE: Topical therapy alone for conjunctivitis is NOT adequate.

2. In children under 9 years of age, in pregnant women and in nursing mothers for uncomplicated urethral, endocervical or rectal infection.

3. In adolescents and adults, when tetracycline or doxycycline is contra-indicated or not tolerated, for uncomplicated urethral, endocervical or rectal infection.

CONTRAI NDICATIONS

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

WARNINGS

Erythromycin should be administered with caution to any patient who has demon started some form of allergy to drugs.

If an allergic reaction to erythrornycin occurs, administration of the drug should be discontinued. Serious hypersensitivity reactions may require epinephrine, antihistamines, or corticosteroids.

There have been reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving erythromycin products. If findings suggestive of significant hepatic dysfunction occur, therapy with erythromycin products should be discontinued.

Pseudomembranous colitis has been occasionally reported to occur in association with erythromycin therapy. Therefore, it is important to consider its diagnosis in patients administered erythromycin that develop diarrhea. Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated. If the colitis is not relieved by discontinuation of erythrornycin administration or when it is severe, consideration should be given to the administration of vancomycin or other suitable therapy. Other possible causes of the colitis should also be considered.

PRECAUTIONS

There have been reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving erythromycin products. If findings suggestive of significant hepatic dysfunction occur, therapy with erythromycin products should be discontinued.

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

Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function.

Drug Interactions

Recent data from studies of erythromycin in patients reveal that its 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.

Erythromycin should be used with caution if administered concomitantly with the following drugs:

- **Lincomycin**
- **Clindamycin**
- **Chloramphenicol**

In vitro experiments have demonstrated that binding sites for erythromycin, lincomycin, clindamycin and chioramphenicol overlap and competitive inhibition may occur.

- **Carbamazepine**
- **Digoxin**

Concomitant administration of erythromycin with carbamazepine or digoxin has been reported to result in elevated plasma levels of these agents, leading to toxicity in some patients.

- **Oral anticoagulants**

Published reports indicate that caution should be observed when some antibiotics, including erythromycin, and oral anticoagulants are used concurrently since prolonged prothrombin time may occur.

• Ergotamine
There are reports that ischemic reactions may occur when erythromycin is given concurrently with ergotamine-containing drugs.

• Cyclosporin
There have been reports that there is a rise in plasma cyclosporin levels during concomitant administration of erythromycin.

Pregnancy
The safety of erythromycin for use during pregnancy has not been established. Erythromycin crosses the placental barrier.

Nursing mothers
The safety of erythromycin for use during breast feeding has not been established. Erythromycin is excreted in breast milk.

Neonates
The safety of erythromycin for use in neonates has not been established.

ADVERSE REACTIONS

Gastrointestinal: abdominal cramping, discomfort. Nausea, vomiting and diarrhea are also observed but less frequently. Pseudomembranous colitis has been occasionally reported to occur in association with erythromycin therapy (see **WARNINGS**).

Allergic reactions: Urticaria, mild skin eruptions and anaphylaxis.

Miscellaneous: During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi and organisms initially sensitive to erythromycin (e.g. *Staphylococcus aureus, Hemophilus influenzae*). If such infections occur, erythromycin should be discontinued and appropriate therapy instituted.

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdose:

Symptoms: In oral doses of over 2 g/day, abdominal discomfort, nausea or diarrhea may occur.

Treatment: There is no specific treatment for overdosage. Erythromycin should be discontinued and gastric lavage should be considered; otherwise, the treatment should be symptomatic.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION

ORAL PREPARATIONS:

Dosage:

Adults:

Upper and lower respiratory tract and skin and soft tissue infections: A therapeutic dosage of oral erythromycin should be administered for at least 10 days. The recommended dosage is 1 g per day given two, three or four times-a-day, depending on the erythromycin preparation chosen. Depending on the severity of infection, larger doses may be considered; however, a single dose should not exceed 1 g.

Primary syphilis: 2 g per day given in divided doses either twice-a-day, three times-a-day or four times-a-day depending on the erythromycin preparation chosen, over a period of 10 to 15 days.

Pertussis: Although optimum dosage and duration of therapy have not been established, doses of erythromycin utilized in reported clinical studies were 40 to 50 mg/kg/day, given in divided doses for 5 to 14 days.

Legionnaires' disease: Although optimal dosages have not been established, doses utilized in reported clinical data were 1 to 4 g daily in divided doses.

Prophylaxis: For prophylaxis against bacterial endocarditis due to alpha-hemo-lytic streptococci in penicillin-allergic patients with valvular heart disease when undergoing dental procedures or surgical procedures of the upper respiratory tract, the adult dose is 1 g orally 1 hour prior to the procedure, and then 500 mg orally 6 hours later. For continuous prophylaxis against recurrences of streptococcal infections in persons with a history of rheumatic heart disease, the dose is 250 mg twice a day.

Children:

Prophylaxis: For prophylaxis against bacterial endocarditis due to alpha-hemolytic streptococci in penicillin-allergic patients with valvular heart disease when undergoing dental procedures or surgical procedures of the upper respiratory tract, the pediatric dose is 20 mg/kg (maximum 1 g) 1 hour before surgery followed by 10 mg/kg (maximum 500 mg) 6 hours later.

Administration:

Adults:

A therapeutic dose of oral erythromycin should be administered for at least 10 days in equally divided doses, two, three or four times-a-day.

EES 600 Tablets 600 mg:

600 mg three times a day regardless of meals. However, maximum blood levels are obtained when **EES 600 Tablets 600 mg** is given immediately after meals.

Children:

Age, weight, and severity of the infection are important factors in determining the proper dosage. The recommended dosage is 30 to 50 mg/kg/day, in divided doses.

Chlamydial Infections:

The 1988 "Canadian Guidelines for the Treatment of Sexually Transmitted Diseases in Neonates, Children, Adolescents and Adults" recommends the following doses of erythromycin:

1. **Conjunctivitis and pneumonia in newborns and infants:** 40 mg/kg/day in four divided doses for at least 14 days.
NOTE: Topical therapy alone for conjunctivitis is NOT adequate.

2. **Uncomplicated urethral, endocervical or rectal infection:**

a) Children under 9 years of age: 40 mg/kg/day orally in four divided doses (up to a maximum of 500 mg q.i.d. for 7 days).

b) Children over 9 years of age when tetracycline or doxycycline is contraindicated or not tolerated: 40 mg/kg/day orally in four divided doses (up to a maximum of 500 mg q.i.d. for 7 days).

c) Pregnant women and nursing mothers: 500 mg orally q.i.d. for 7 days or 250 mg orally q.i.d. for 14 days if the larger dose is not tolerated.

d) Adolescents and adults when tetracycline or doxycycline is contraindicated or not tolerated: 500 mg q.i.d. for 7 days.

3. **Complicated infection:** The duration of treatment should be for at least 10 days.

As with all sexually transmitted diseases, follow up cultures after termination of therapy are recommended in order to assess the microbiological response.

PHARMACEUTICAL INFORMATION

CHEMISTRY

Trade Names:

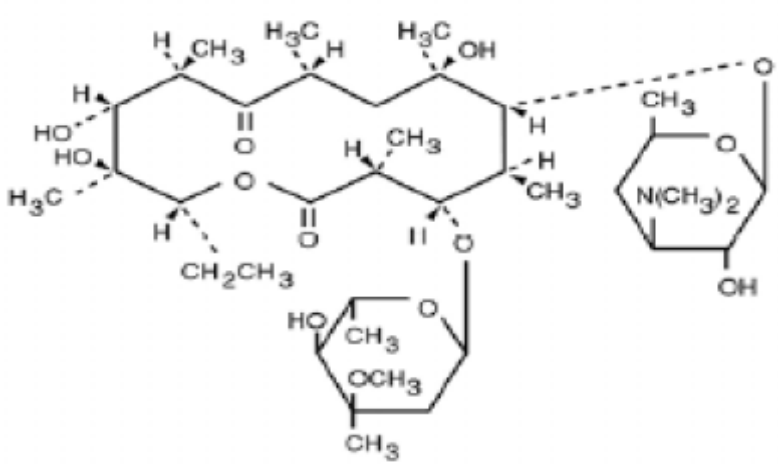
1. EES 600 Tablets 600 mg

No.	Proper Name	Molecular Formula	Molecular Weight
1.	Erythromycin ethylsuccinate tablets USP	$C_{43}H_{75}NO_{16}$	862.06

Chemical Name (erythromycin free base):

(3R*,4S*,5S*,6R*,7R*,9R*,11R*,12R*,13S*,14R*)-4-[(2,6-dideoxy-3-C-methyl-3-0-methyl-α-L-ribo-hexopyranosyl)-oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy] oxacyclotetradecane-2, l0-dione.

Structural formula:



Description:

Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. It occurs as white or slightly yellow, odorless or almost odorless, slightly hygroscopic crystals or powder with a bitter taste. It is freely soluble in methanol, ethanol, acetone and chloroform. It is soluble in water at 2 mg/mL. The melting point is l35-l40^{o}C.

Erythromycin ethylsuccinate is an ester of erythromycin, soluble in most organic solvents, but poorly soluble in water.

Composition:

EES 600 Tablets 600 mg contains erythromycin ethylsuccinate (expressed in terms of free base).

Oral Preparations:

EES 600 Tablets 600 mg (erythromycin ethylsuccinate tablets USP) is supplied as Filmtab tablets containing 600 my erythromycin.

MICROBIOLOGY

Many strains of *Hemophilus influenzae* are resistant to erythromycin alone.

Staphylococci resistant to erythromycin may emerge during a course of erythromycin therapy. Culture and sensitivity testing should be performed prior to and during therapy.

Erythromycin is usually bacteriostatic but may be bactericidal in high concentrations. The bactericidal activity is greatest against a small number of rapidly dividing microorganisms and increases markedly as the pH of the medium is raised over the range of pH 5.5 to 8.5.

The in vitro activity of erythromycin against various microorganisms is presented in Table 1.

Table 1

IN VITRO SUSCEPTIBILITY OF 750 STRAINS OF

GRAM - POSITIVE AND GRAM - NEGATIVE BACTERIA TO ERYTHROMYCIN

MICROORGANISMS	NUMBER OF STRAINS	CUMULATIVE % OF STRAINS INHIBITED AT MIC (mg/L)											
		.015	.031	.062	.125	.250	.500	1.00	2.00	4.00	8.00	16.00	32.00	64.00
Gram-Positive														
Staphylococcus aureus	151	-	-	-	38	66	70	72	72	72	72	72	74	100
Staphylococcus epidermidis	59	-	1	5	32	44	44	45	45	45	45	45	50	100
Other coagulase negative staphylococcus	27	-	-	-	33	44	48	48	48	48	48	48	59	100
Streptococcus pyogenes (Gr A)	48	-	83	89	91	91	95	95	97	100	-	-	-	-
Streptococcus pneumoniae	26	-	30	61	84	84	84	100	-	-	-	-	-	-
Streptococcus agalactiae (Gr D)	41	-	95	95	95	95	95	95	97	100	-	-	-	-
Streptococcus viridans	15	-	80	86	86	93	93	93	93	93	93	93	93	100
Enterococcus	97	-	-	2	7	11	36	59	60	60	64	67	68	100
Other β-hemolytic Streptococcus	19	-	68	78	78	78	84	84	84	89	89	89	94	100
Corynebacterium species	11	-	18	36	45	45	54	54	54	81	81	90	90	100
Corynebacterium diphtheriae	35	-	90	-	-	-	-	-	-	-	-	-	-	-
Listeria monocytogenes	7	-	-	42	100	-	-	-	-	-	-	-	-	-
Gram-Negative														
Neisseria gonorrhoeae	39	-	20	35	66	100	-	-	-	-	-	-	-	-
Neisseria meningitidis	6	-	-	-	-	66	83	100	-	-	-	-	-	-
Haemophilus influenzae	56	-	1	3	3	10	25	58	100	-	-	-	-	-
Campylobacter species	30	-	-	-	10	36	80	96	100	-	-	-	-	-
Bordetella pertussis	50	50	90	-	-	-	-	-	-	-	-	-	-	-
Legionella pneumophila	33	-	-	50	-	90	-	-	-	-	-	-	-	-

Susceptibility Testing:

The standard single disc susceptibility test (using the 15 ug erythromycin disc) and the dilution susceptibility test should be interpreted according to the criteria in table 2.

Table 2

Criteria for Interpreting Standard Single Disc Susceptibility Test and The Dilution Susceptibility Test		
	Zone Diameter (mm)	**Approximate MIC Correlate (mg/L)**
Susceptible	$\geq$ 18	$\leq$ 2
Intermediate*	14-17	-
Resistant	$\leq$ 13	$\geq$ 8
* Indicates that the test results are equivocal; therefore, dilution tests may be indicated. N.B.: These criteria and the definition are in agreement with NCCLS Order Code M2A3.		

Control limits for monitoring erythromycin susceptibility tests are given in Table 3.

Table 3

Control Limits for Monitoring Erythromycin Susceptibility Tests

	Zone Diameter (mm)	**MIC (mg/L)**
S. aureus ATCC 29213	22-30	0.12 - 0.50
S. faecalis ATCC 29212		1.0 - 4.0

PHARMACOLOGY

Orally administered erythromycin base and its salts are absorbed in the microbiologically active form. Significant inter-individual variations in the absorption of erythromycin were observed and some patients do not achieve maximal serum levels.

Erythromycin is largely bound to plasma proteins (over 70%).

In the presence of normal hepatic function, erythromycin is concentrated in the liver and is excreted in the bile; the effect of hepatic dysfunction on bilary excretion of erythromycin is not known.
From 12 to 15 percent of intravenously administered erythromycin is excreted in active form in the urine. After oral administration, less than 5% of the administered dose can be recovered in the active form in the urine.

Pharmacokinetics:

Oral administration:

Representative erythromycin pharmacokinetic parameters (Cmax, Tmax and AUC, with standard deviation) obtained from studies using different erythromycin preparations are listed in Table 4. Due to large inter-individual variations, it must be cautioned that direct comparisons cannot be made between different studies and also different erythromycin derivatives.

Table 4

DEMOGRAPHIC INFORMATION AND MEAN (± SD) PHARMACOKINETIC PARAMETERS FOR ERYTHROMYCIN DERIVATIVES ADMINISTERED AS A SINGLE DOSE IN THE ABSENCE OF FOOD

VARIABLE	ERYTHROMYCIN DERIVATIVES					
	ERYTHROMID* (erythromycin tablets USP)	ERY-TAB* (erythromycin delayed-release tablets USP)	ERYTHROMYCIN Delayed-Release Capsules USP)	PCE* (particle coated erythromycin tablets)	ERYTHROCIN* (erythromycin stearate tablets USP)	EES* (erythromycin ethylsuccinate tablets USP)
No. of male Patients	22	24	23[1]	24	20	20
Age (year)	-	26.7 ± 5.7	36 ± 8	25 ± 5	23.4	23.4
Weight (kg)	-	76.7 ± 8.6	71.8 ± 10.9	73 ± 6.9	72.5	72.5
Dose (mg)	250	500	250	333	500	600
C_{max} (mg/L)	0.93 ± 0.58	1.68 ± 1.12	1.15 ± 0.51	1.52 ± 0.86	1.80 ± 1.02	1.03 ± 0.62
C_{max}/100 mg[2]	0.37	0.34	0.46	0.46	0.36	0.17
T_{max} (hr)	2	4	2.9	3	1.7	1.2
AUC mg.hr/L	2.06 ± 1.23[3]	6.06 ± 2.46[4]	3.48 ± 1.75[4]	4.24 ± 2.56[4]	4.18 ± 1.77[5]	2.28 ± 1.28[5]
AUC/100 mg[2]	0.82	1.21	1.39	1.27	0.84	0.38

[1] 12 males and 11 females

[2] $C_{max}/100\ mg = C_{max} \times \frac{100\ mg}{dose}$, $AUC/100\ mg = AUC \times \frac{100\ mg}{dose}$

[3] $AUC_{0-6\ hr}$

[4] $AUC_{0-12\ hr}$

[5] $AUC_{0-8\ hr}$

EES 600 Tablets 600 mg- Erythromycin ethylsuccinate (600 mg) was administered orally to 20 adult male volunteers (mean age = 23.4 years and mean weight = 72.5 kg) under fasting and non-fasting condition in a crossover design study. The mean fasting Cmax (mg/L), Tmax (hr) and AUC_{0-8} hr (mg.hr/L) were 1.03, 1.2 and 2.28, respectively (see Table 4). The mean non-fasting Cmax (mg/L), Tmax (hr) and AUC $_{0-8}$ hr (mg.hr/L) were 1.17, 1.3 and 2.72, respectively.

TOX ICOLOGY

Acute Toxicity:

The acute toxicity of erythromycin administered by a variety of routes was studied in mice and rats (see Table 5 below).

Table 5

Acute L5D0 Values of Erythromycin

	L5D0 Value in mg/kg	
Route	MICE	RATS
I.V.	426	209
I.M.	394	-
P.O.	3112	9227

Chronic Toxicity:

A chronic toxicity study with erythromycin base was performed in dogs and rats. Dogs were administered dosages ranging up to 100 mg/kg/day for a period up to 90 weeks. Rats were given up to 4 g/kg/day for a period up to 85 weeks.

A review of the clinical signs and symptoms, weight curves, clinical laboratory values and gross and microscopic findings showed no evidence of toxicity due to drug action in dogs and rats at the dose levels indicated.

Teratology Studies:

There was no evidence of teratogenicity or other adverse effects on reproduction in female rats fed erythromycin base (up to 0.25 percent of diet) prior to and during mating, during gestation and through weaning of two successive litters.

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