PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrERYC®

(Erythromycin delayed release capsules USP)

333 mg

Antibiotic

Pfizer Canada ULC

17,300 Trans-Canada Highway

Kirkland, Quebec H9J 2M5

Date of Initial Authorization:
SEP 30, 1983

Date of Revision:

April 21, 2022

Submission Control Number: 258552

RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	09/2021
7 WARNINGS AND PRECAUTIONS, Cardiovascular	09/2021
7.1.3 Pediatrics	09/2021

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ERYC (Erythromycin Capsules) is indicated for the treatment of the following infections caused by susceptible strains of the designated microorganisms:

- **Upper Respiratory Tract Infections**: those of mild to moderate severity caused by *Streptococcus pyogenes* (group A beta-hemolytic *streptococci*); *Streptococcus pneumoniae* (*Diplococcus pneumoniae*); and *Hemophilus influenzae*. Not all strains of *Hemophilus influenzae* are susceptible to erythromycin with usual therapeutic doses.
- **Lower Respiratory Tract Infections**: those of mild to moderate severity when caused by *Streptococcus pyogenes* (group A beta-hemolytic *streptococci*); *Streptococcus pneumoniae* (*Diplococcus pneumoniae*); and *Mycoplasma pneumoniae* (Eaton's agent).

Pertussis (Whooping Cough): caused by *Bordetella pertussis*. Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them non-infectious. Clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Diphtheria: As an adjunct to antitoxin in infections due to *Corynebacterium diphtheriae*, to prevent establishment of carriers and to eradicate the organism in carriers.

Legionnaires' Disease: caused by *Legionella pneumophila*. Controlled clinical efficacy studies have not been conducted. In vitro and limited preliminary clinical data suggest that erythromycin can be effective in the treatment of Legionnaires' disease.

- **Skin and Soft Tissue Infections:** those of mild to moderate severity when caused by *Streptococcus pyogenes* and *Staphylococcus aureus* (resistance of *staphylococci* may emerge during treatment).

Erythrasma: in the treatment of infections due to *Corynebacterium minutissimum*.

The treatment of *Acne vulgaris*.

- **Sexually Transmitted Diseases:**

Primary Syphilis: caused by *Treponema pallidum*. Erythromycin is an alternate choice for treatment for primary syphilis in patients allergic to the penicillins. Spinal fluid should be examined before treatment and as part of the follow-up after therapy.

Chlamydia Trachomatis Infection: Erythromycin is an alternate choice in the treatment of the following infections when caused by Chlamydia trachomatis:

a) In infants and children (9 years and older) for conjunctivitis.

NOTE: Topical therapy alone for conjunctivitis is NOT adequate.

b) In pregnant women and nursing mothers for urethral, endocervical or rectal infections.

c) In youths and adults, for urethral, endocervical or rectal infections.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ERYC and other antibacterial drugs, ERYC should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they

should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

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.

1.1 Pediatrics

Neonates: The safety and efficacy of ERYC has not been established. Therefore, Health Canada has not authorized an indication in neonates (see **7.1.3 Pediatrics**).

Further pediatric information can be found in the following sections, see **1 INDICATIONS**, **4.2 Recommended Dose and Dosage Adjustment**, and **7.1.3 Pediatrics.**

1.2 Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see **7.1.4 Geriatrics)**.

2 CONTRAINDICATIONS

- Erythromycin Capsules is contraindicated in patients with known hypersensitivity to erythromycin or the product's components, with infections caused by microorganisms that are resistant to the drug.
- Erythromycin Capsules is contraindicated with co-administration of terfenadine, astemizole, pimozide, ergotamine, dihydroergotamine or cisapride. There have been post-marketing reports of drug interactions when erythromycin is co-administered with cisapride, astemizole, pimozide or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of hepatic metabolism of these drugs by erythromycin. Fatalities have been reported (see **7 WARNINGS AND PRECAUTIONS, 9 DRUG INTERACTIONS**).
- Do not use ERYC (Erythromycin Capsules) concomitantly with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) that are extensively metabolized by cytochrome P450 isoform 3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis (see **7 WARNINGS AND PRECAUTIONS, 9 DRUG INTERACTIONS**).

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Adults: The usual dose is 333 mg every 8 hours. Dosage may be increased up to 4 g per day, depending on the severity of infection. Twice-a-day dosing is not recommended when doses larger than 1 g daily are administered.

Children: Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual dosage is 30-50 mg/kg/day in equally divided doses. For the treatment of more severe infections, this dosage may be doubled.

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 in divided doses (2, 3, or 4 times a day), depending on the erythromycin preparation chosen. Depending on the severity of infection, doses up to 4 g may be considered; however, a single dose should not exceed 1 g.
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: Large doses of up to 4 g daily in divided doses are necessary for the treatment of known or suspected Legionella infections.

Acne Vulgaris: Initially, up to 1 g per day is given in divided doses. Depending on clinical response this may then be reduced to 333 per day as a maintenance dose. Extended administration of erythromycin requires regular evaluation, particularly of liver function.

Chlamydia Trachomatis Infections:

1. Conjunctivitis in infants and children:
Infants > 2000 g: 30 mg/kg/day orally in divided doses for at least 14 days.
Infants > 1 week to 1 month: 40 mg/kg/day orally in divided doses for at least 14 days.
Children 9 years or older as alternative treatment: 40 mg/kg/day orally in divided doses (max. 2000 mg per day for 7 days or 1000 mg per day for 14 days).
NOTE: Topical therapy alone for conjunctivitis is NOT adequate.
2. Urethral, endocervical, rectal infection in pregnant women and nursing mothers: 2 g/day orally in divided doses for 7 days.
3. Youth and adults: urethral, endocervical, rectal infection: 2 g/day orally in divided doses for 7 days.

NOTE: Erythromycin dosages refer to the use of erythromycin base. Equivalent dosages of other formulations (EXCEPT the estolate which is contraindicated in pregnancy) may be substituted. If erythromycin has been used for treatment, repeat testing after completion of therapy is advisable.
As with all sexually transmitted diseases, follow up cultures after termination of therapy are recommended in order to assess the microbiological response.

Primary Syphilis: 2-4 g per day given in divided doses either 2, 3 or 4 times-a-day depending on the erythromycin preparation chosen, over a period of 10 to 15 days (see **7.1.3 Pediatrics**).

Prophylaxis: Erythromycin can also be used for continuous prophylaxis against recurrence of streptococcal infections in adults with a history of rheumatic heart disease.

4.4 Administration

ERYC should be given orally at least 30 minutes and preferably 2 hours before or after a meal (see 9**.5 Drug-Food Interactions**).

5 OVERDOSAGE

With oral doses of over 2 grams per day, hearing loss, abdominal discomfort, nausea or diarrhea may occur. There has been a report of a case of erythromycin-induced pancreatitis following erythromycin overdose. There is no specific treatment for overdosage. ERYC should be discontinued and prompt elimination of unabsorbed drug and all other appropriate measures should be considered which may include use of activated charcoal; otherwise, treatment should be symptomatic. Erythromycin is not removed by peritoneal dialysis or hemodialysis.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	ERYC 333 is a two-tone clear and opaque yellow capsule containing 333 mg erythromycin base as enteric-coated pellets. Available in bottles of 100.	*ERYC 333:* Non-medicinal ingredients: cellulose acetate phthalate, diethyl phthalate, lactose, methanol, methylene chloride, potassium phosphate monobasic and povidone. Capsule shell: D&C Yellow No. 10, D&C Red No. 33, gelatin and titanium dioxide. Gluten-, paraben- and tartrazine-free. Imprinted "ERYC 333 mg" and "Pfizer".

7 WARNINGS AND PRECAUTIONS

General

Prescribing ERYC in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

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

Cardiovascular

QT Prolongation and Arrhythmias

Life-threatening episodes of ventricular tachycardia associated with prolonged QT interval (torsades de pointes) have been reported in some patients treated with macrolides, including erythromycin.

Susceptibility to the development of torsades de pointes is related to cardiovascular disease (including a history of QT prolongation), electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia), hepatic dysfunction, and concurrent medical products associated with QT prolongation (see **9 DRUG INTERACTIONS**).

Erythromycin should be used with caution in patients with these risk factors. Elderly patients who are at greater risk of decreased hepatic and cardiac function, concomitant disease and drug therapy, should be carefully monitored during erythromycin treatment (see **8.1 ADVERSE REACTIONS OVERVIEW**).

Gastrointestinal

Clostridium difficile-associated disease (CDAD):

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including ERYC (erythromycin). CDAD may range in severity from mild diarrhoea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhoea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of Clostridium difficile. C. difficile produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against Clostridium difficile. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against Clostridium difficile. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see 8 **ADVERSE REACTIONS Overview**).

Hepatic/Biliary/Pancreatic

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

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

Immune

Erythromycin should be administered with caution to any patient who has demonstrated some form of allergy to drugs. If an allergic reaction to erythromycin occurs, administration of the drug should be discontinued. Serious hypersensitivity reactions may require epinephrine, antihistamines, or corticosteroids.

Monitoring and Laboratory Tests

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

Musculoskeletal

- The risk of myopathy during treatment with certain HMG-CoA reductase inhibitors is increased with concomitant administration of erythromycin. Physicians considering combined therapy should carefully weigh the potential benefits and risks and monitor patients for any signs and symptoms of muscle pain, tenderness or weakness (see **7 WARNINGS AND PRECAUTIONS, 9 DRUG INTERACTIONS**).
- Exacerbation of symptoms of myasthenia gravis and new onset of symptoms of myasthenic

syndrome has been reported in patients receiving erythromycin therapy.

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

7.1 Special Populations

7.1.1 Pregnant Women

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

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

The safety and efficacy of ERYC for use in neonates has not been established.

Infants born to women treated during pregnancy with oral erythromycin for early syphilis should be treated with an appropriate penicillin regimen since erythromycin does not reach the fetus in adequate concentration.

Infantile hypertrophic pyloric stenosis:

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in neonates and 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 neonates and infants. This risk is higher 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 neonates and 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.

7.1.4 Geriatrics

Clinical studies with ERYC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of the decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

There have been reports of prolonged QT syndrome in geriatric patients receiving erythromycin products.

Elderly patients may experience increased effects of oral anticoagulant therapy while undergoing treatment with erythromycin (see **7 WARNINGS AND PRECAUTIONS, 9 DRUG INTERACTIONS**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Cardiovascular: QT prolongation, ventricular tachycardia, and torsades de pointes have been reported with macrolides, including erythromycin (see **2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, 9 DRUG INTERACTIONS**).

Gastrointestinal: Abdominal cramping and discomfort have been observed. Nausea, vomiting and diarrhea are also observed, but less frequently. Clostridium difficile-associated disease, pseudomembranous colitis and pyloric stenosis have been observed (see **7 WARNINGS AND PRECAUTIONS**).

Pancreatitis: There has been a report of a case of erythromycin-induced pancreatitis following erythromycin overdose.

Skin: Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Allergic Reactions: Urticaria, mild skin eruptions and anaphylaxis have been reported.

Hepatotoxicity: There have been reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving erythromycin products.

Renal: Tubulointerstitial nephritis has been reported.

During prolonged or repeated therapy, there is a possibility of overgrowth of non-susceptible 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. Deafness has been reported.

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

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Terfenadine: Terfenadine undergoes metabolism in the liver by a specific cytochrome P450 isoenzyme. This metabolic pathway may be impaired in patients who are taking erythromycin, an inhibitor of this isoenzyme. Interference with this enzyme can lead to elevated terfenadine plasma levels which may be associated with QT prolongation, and increased risk of ventricular tachyarrhythmias (such as torsades de pointes, ventricular tachycardia, and ventricular fibrillation) (see **2 CONTRAINDICATIONS**).

Astemizole: Concomitant administration of astemizole with erythromycin is contraindicated because 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 astemizole with erythromycin. In each case the QT intervals were prolonged beyond 650 milliseconds at the time of the event; one patient also received ketoconazole and the other patient also had hypokalemia (see **2 CONTRAINDICATIONS**).

Rare cases of serious cardiovascular adverse events, including death, cardiac arrest and other ventricular arrhythmias have been observed.

Theophylline: The concomitant administration of erythromycin and high doses of theophylline may be associated with increased serum theophylline levels and possible theophylline toxicity. The dose of theophylline may require reduction while patients are receiving ERYC.

Carbamazepine: Erythromycin administration in patients receiving carbamazepine has been reported to cause increased serum levels of carbamazepine with subsequent development of signs of carbamazepine toxicity.

Digoxin/Phenytoin: Concomitant administration of erythromycin and digoxin or phenytoin has been reported to result in elevated serum levels of these agents, leading to toxicity in some patients.

Oral Anticoagulants: There have been reports of increased prothrombin time when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to this drug may be more pronounced in the elderly (see **7.1.4 Geriatrics**).

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

Cyclosporin: A rise in plasma cyclosporin levels has been reported during concomitant administration of erythromycin.

Lincomycin/Clindamycin/Chloramphenicol: Erythromycin should be used with caution if administered concomitantly with lincomycin, clindamycin, or chloramphenicol. *In vitro* experiments have demonstrated that binding sites for erythromycin, lincomycin, clindamycin and chloramphenicol overlap and competitive inhibition may occur.

Triazolam/Midazolam: Erythromycin has been reported to decrease the clearance of triazolam and midazolam and thus may increase the pharmacologic effect of these drugs.

Alfentanil: The concomitant use of erythromycin with alfentanil can significantly inhibit the clearance of alfentanil and may increase the risk of prolonged or delayed respiratory depression.

Lovastatin/Simvastatin: Erythromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g. lovastatin or simvastatin) (see **2 CONTRAINDICATIONS**). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Cisapride/Pimozide: Rare cases of serious cardiovascular adverse events, including death, cardiac arrest, torsades de pointes, and other ventricular arrhythmias have been observed in patients taking cisapride concomitantly with macrolide antibiotics including erythromycin.

Atorvastatin: In healthy individuals, coadministration of erythromycin (500 mg QID) was associated with higher plasma concentrations of atorvastatin.

Quinidine: Drug interaction occurring with the concomitant administration of erythromycin and quinidine in their usual oral forms, resulting in QT prolongation, torsades de pointes and cardiac arrest has been reported. Caution and close monitoring are recommended when the drugs are administered

concomitantly.

Verapamil: Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients receiving concurrent verapamil, a calcium-channel blocker.

Cimetidine: Cimetidine may inhibit the metabolism of erythromycin, which may lead to an increased plasma concentration.

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

The use of erythromycin in patients taking concurrent drugs which are metabolized by cytochrome P450 (3A4) system may be associated with elevations in serum levels of these other drugs (e.g. pimozide, ergotamine, dihydroergotamine) (see **2 CONTRAINDICATIONS**). There have been reports of interactions of erythromycin with cyclosporine, tacrolimus, hexobarbital and phenytoin. Serum concentrations of drugs metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin.

9.5 Drug-Food Interactions

Blood levels obtained upon administration of ERYC (enteric-coated erythromycin pellets) in the presence of food are above minimum inhibitory concentrations (MIC's) of most organisms for which erythromycin is indicated. However, maximum blood levels are obtained in the fasting state (at least 30 minutes and preferably 2 hours before or after a meal).

9.6 Drug-Herb Interactions

The effects of herbal products on the pharmacokinetics of Erythromycin have not been studied.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of action

Erythromycin exerts its antibacterial action by binding with the 50S ribosomal subunit of the organism, inhibiting peptide bond formation and protein synthesis within the bacterial cell. The activity is bacteriostatic or bactericidal depending on concentration.

10.3 Pharmacokinetics

Absorption

The enteric coating of pellets in ERYC capsules protects the erythromycin base from inactivation by gastric acidity. Because of their small size and enteric coating, the pellets may pass intact from the stomach to the small intestine and dissolve efficiently to allow absorption of erythromycin in a uniform manner.

Following oral administration, erythromycin base is readily absorbed from the upper part of the small

intestine in the microbiologically active form. The drug is largely bound to plasma proteins, and the freely dissociating bound fraction after administration of erythromycin base represents 90% of the total erythromycin absorbed.

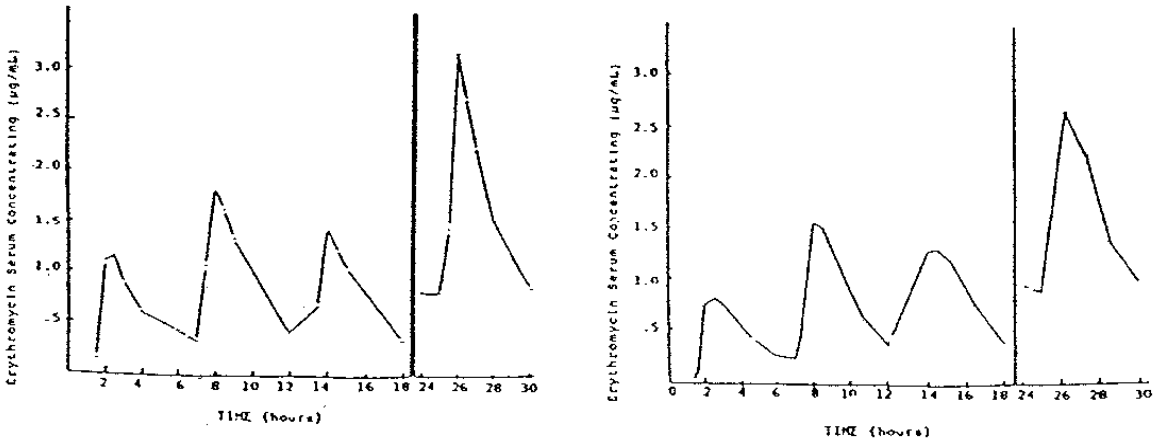
Bioavailability

Effect of Fasting: Bioavailability studies of ERYC capsules have been conducted in the fasting and non-fasting states. Single 250 mg doses were administered at 0, 6, 12, 18 and 24 hours. In one group (n=24), doses 1,2,3 and 5 were taken one hour before meals; the fourth dose was taken without food (Figure 1A). In a second group dosing similarly occurred five times at 6 hours intervals, but immediately before or after eating (Figure 1B). It was found that ERYC capsules, when taken immediately before or after meals, demonstrate a decrease in bioavailability compared with the levels achieved when they are taken during fasting states.

Figure 1: Serum Concentrations of Erythromycin

Following Administration of ERYC Capsules, 250 mg

1A: FASTING **1B: NON-FASTING**



Effect of Dosage Form: Three comparative multiple-dose bioavailability studies were performed to evaluate the efficacy and reliability in absorption of erythromycin from ERYC capsules versus enteric-coated tablets and film-coated stearate tablets. Five doses of 250 mg were given 6-hours apart and serum levels of erythromycin were analyzed in 24-26 volunteers in each study. ERYC capsules gave a better and more reliable absorption than enteric-coated tablets and film-coated stearate tablets, whether the stearate was given 1 hour before food or immediately before a meal. Significant inter-individual variations in the absorption of erythromycin were observed and some patients did not achieve maximal serum levels.

ERYC 250: Erythromycin serum levels were determined in 27 subjects following oral administration of a single 250 mg or 500 mg dose of ERYC 250 under fasting conditions. Mean pharmacokinetic parameters are reported in Table 2.

TABLE 2: Mean (SD) Pharmacokinetic Parameters After Administration of ERYC 250 Capsules in the Fasting State

Parameter	ERYC 250 Treatment

	1x250 mg Capsule		2x250 mg Capsules	
AUC_{0-16} (hr.mg/mL)	4.85	(1.71)	11.60	(4.43)
C_{max} (mg/mL)	1.39	(0.43)	2.73	(0.84)
T_{max} (hr)	3.67	(1.35)	4.00	(1.06)
K_{el} (hr^{-1})	0.403	(0.098)	0.389	(0.063)
$t_{1/2}$ (hr)	1.81	(0.41)	1.83	(0.31)

0

ERYC 333: A multidose study in 23 subjects receiving 1 capsule of ERYC 333 every 8 hours (5 doses) or 1 capsule of ERYC 250 every 6 hours (6 doses) produced average steady-state concentrations (0.89 vs. 0.92 mg/L) and normalized AUC's (10.69 vs. 11.06 hr.mg/L) which were not significantly different for the 2 dosing regimens.

Distribution:

After absorption, erythromycin diffuses readily into most body fluids. In the absence of meningeal inflammation, low concentrations are normally achieved in the spinal fluid, but passage of the drug across the blood-brain barrier increases in meningitis. Erythromycin is excreted in breast milk. The drug crosses the placental barrier, but fetal plasma levels are low.

Elimination

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 biliary excretion of erythromycin is not known. After oral administration less than 5% of the administered dose can be recovered in the active form in the urine.

The half-life (t½) for erythromycin is approximately 2 hours.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature below 30°C. Protect from moisture and light.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions required.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

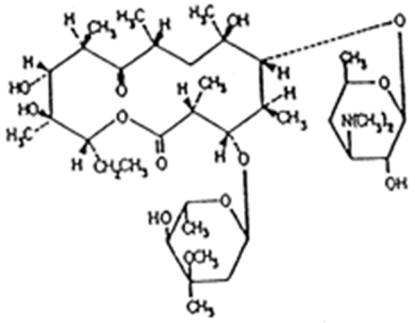
Drug Substance

Proper name: Erythromycin

Chemical name: (3R*,4S*,5S*,6R*,7R*,9R*,11R*,12R*,13S*,14R*)-4-[(2,6-Dideoxy-3-C-methyl-3-O-methyl- L-ribo-hexopyranosyl)-oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-b-D-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione.

Molecular formula and molecular mass: $C_{37}H_{67}NO_{13,}$ 734

Structural formula:



Physicochemical properties: 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 135-140°C.

14 CLINICAL TRIALS

The clinical trial data on which the original indications were authorized are not available.

15 MICROBIOLOGY

The in vitro activity of erythromycin against various microorganisms is shown in Table 3 below:

TABLE 3: In Vitro Spectrum of Erythromycin Activity

Organism	Typical Minimum Inhibitory Concentration (mcg/mL) Mean	Range		
Gram-positive cocci:				
Staphylococcus aureus	0.4	0.005	-	>100
Streptococcus pyogenes	0.04	0.005	-	0.8
Streptococcus pneumoniae	0.05	0.006	-	0.2
Streptococcus viridans	0.06	0.02	-	0.1
Enterococcus	1.5	0.1	-	>400
Gram-positive bacilli:				
Clostridium perfringens	0.5	0.5	-	5
Corynebacterium diphtheriae	0.02	0.006	-	0.2
Listeria monocytogenes	0.16	0.1	-	0.3
Gram-negative cocci and bacilli:				
Neisseria gonorroheae	0.1	0.005	-	0.4
Neisseria meningitidis	0.4	0.1	-	0.8
Hemophilus influenzae	3.1	0.1	-	6
Bordetella pertussis	0.3	0.02	-	1.56
Bacteroides fragilis	1.5	0.12	-	>128
Brucella species	5	0.3	-	10
Legionella pneumophila	<0.5		-	
Others:				
Actinomyces israelii	0.5	0.2	-	0.5
Nocardia asteroides	25	0.2	-	>200
Mycoplasma pneumoniae	0.005	0.001	-	0.01
Mycobacterium kansasii	1	0.5	-	2

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.

Susceptibility Testing

The standard single-disc susceptibility test using a 15 mg erythromycin disc and the dilution susceptibility test should be interpreted according to the criteria in Table 4:

TABLE 4

	Zone Diameter (mm)	Approximate MIC Correlate (mg/L)
Susceptible	>18	<2
Intermediate*	14 - 17	-
Resistant	<13	>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 5.

TABLE 5

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

16 NON-CLINICAL TOXICOLOGY

The acute toxicity of erythromycin base (LD_{50}) is reported to be as follows in Table 6:

Table 6: Acute Toxicity of Erythromycin Base (LD_{50})

Animal Species	Route of Administration	LD_{50} Value (mg/kg)
Mouse	P.O.	3112
	S.C.	>2500
Rat	P.O.	>3000
	S.C.	>2000
Guinea Pig	I.P.	413
Hamster	P.O.	3018

Chronic Toxicity

A chronic toxicity study with erythromycin base was performed in dogs and rats. Dogs were administered doses 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 drug-related toxicity in dogs or rats at the dose levels indicated.

Reproductive and Developmental Toxicology: There was no evidence of teratogenicity or other adverse effects on reproduction in female rats fed erythromycin base (up to 0.25% of diet) prior to and during mating, during gestation and through weaning of 2 successive litters.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ERYC

Erythromycin delayed release capsules USP

Read this carefully before you start taking **ERYC** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ERYC**.

What is ERYC used for?

ERYC treats certain bacterial infections:

- of the lungs and throat (respiratory tract).
- of skin and other soft tissue, including acne.
- passed during sex (e.g. syphilis and chlamydia).

Antibacterial drugs like ERYC treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, ERYC should be used exactly as directed. Misuse or overuse of ERYC could lead to the growth of bacteria that will not be killed by ERYC (resistance). This means that ERYC may not work for you in the future. Do not share your medicine.

How does ERYC work?

ERYC is an antibiotic. It works by killing or stopping the growth of the bacteria that cause your infection.

What are the ingredients in ERYC?

Medicinal ingredients: Erythromycin

Non-medicinal ingredients: cellulose acetate phthalate, diethyl phthalate, lactose, methanol, methylene chloride, potassium phosphate monobasic and povidone. Gluten-, paraben- and tartrazine-free.

Capsule shell of **ERYC** 333 mg: D&C Yellow No. 10, D&C Red No. 33, gelatin and titanium dioxide.

ERYC comes in the following dosage forms:

- Capsules: 333 mg

Do not use ERYC if you:

- are allergic to erythromycin or any other ingredients of ERYC (see What are the ingredients in ERYC?).
- are taking any of the following medication:
  - dihydroergotamine, ergotamine (for migraine).
  - cisapride* (for stomach problems).
  - astemizole* and terfenadine* (antihistamines, for treating allergies).
  - pimozide (for psychiatric problems).
  - lovastatin, simvastatin (for reducing blood cholesterol).

    * no longer marketed in Canada

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ERYC. Talk about any health conditions or problems you may have, including if you:

- have liver problems.
- have myasthenia gravis (a disease which causes muscle weakness, difficulty chewing and swallowing and slurred speech).
- have an irregular heartbeat, especially a problem called QT prolongation.
- are pregnant or planning to become pregnant.
- are breastfeeding or planning to breastfeed. Erythromycin is passed to the infant through human breast milk

Other warnings you should know about:

While taking **ERYC**

- Follow your doctor's instructions carefully.
- Tell your doctor and pharmacist that you are taking ERYC if you are about to start taking any new medicines.
- Do not stop taking your medicine until your doctor tells you to, even if you are feeling better.

Do not use **ERYC** to treat any other medical complaints unless your doctor tells you to.

If you develop diarrhea during or after treatment with **ERYC**, tell your doctor at once. Do not use any medicine to treat your diarrhea without first checking with your doctor.

Contact your doctor if your baby vomits or is irritable while being fed.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ERYC:

- alfentanil, midazolam, zopiclone and triazolam (sedatives which may be given before an operation).
- astemizole* and terfenadine* (antihistamines, for treating allergies).
- atorvastatin (for reducing blood cholesterol).
- carbamazepine, hexobarbital, phenytoin (for epilepsy).
- chloramphenicol, clindamycin and lincomycin (for infections).
- cyclosporin (for prevention of rejection after graft or organ transplant).
- cisapride* and cimetidine (for stomach problems).
- digoxin and quinidine (for heart conditions).
- dihydroergotamine, ergotamine (for migraine).
- oral anticoagulants (for preventing blood clots).
- pimozide (for psychiatric problems).
- theophylline (for breathing problems).
- verapamil (for high blood pressure).

* no longer marketed in Canada

How to take ERYC:

Follow your doctor's instructions carefully about how much ERYC to take and when to take it.
ERYC should be swallowed, at least 30 minutes and preferably 2 hours before or after a meal.
ERYC 333 mg capsules is not recommended for sprinkling, since the capsules are very full and some of the medication may be lost through spillage. If, however, the capsule is to be opened, care must be taken to open the capsule over food so as not to lose any of the pellets.

1. Hold the capsule with the clear end down. Gently twist off the orange cap to open.
2. Sprinkle the ENTIRE contents of the capsule on a spoonful of applesauce, fruit jellies, ice cream, etc. The pellets should not be chewed or crushed.
3. Have your child swallow the spoonful of applesauce, fruit jellies, or ice cream. Your child should drink some water to make sure all the pellets are swallowed.
4. If the pellets are accidentally spilled, start over with a new capsule.

Usual dose:

Adult dose:

- one capsule of 333 mg three times a day

Your doctor may decide to increase the dose depending on the specific condition you have.

Child dose:

Your child's doctor will decide the dose of ERYC to give to your child, depending on your child's age, weight and on the specific condition your child has.

Overdose:

Do not take more capsules than your doctor has told you to.

If you think you, or a person you are caring for, have taken too much **ERYC**, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you should forget to take your capsule at the usual time, take it as soon as you remember unless it is time to take the next one. Continue with the remaining doses as before. Do not take more than one dose at a time.

What are possible side effects from using ERYC?

These are not all the possible side effects you may have when taking **ERYC**. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Nausea.
- Vomiting.
- Stomach pain and discomfort.
- Diarrhea.
- Itching and skin rashes.
- Confusion.

- Hallucinations.
- Vertigo (dizziness, balance problem).
- Seizure.
- Problems with your pancreas.
- Problems with your kidneys.
- Hearing problems.
- Muscle pain and weakness.

If they occur, they are likely to be minor and temporary. However, some may be serious and need medical attention.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON **Clostridium difficile colitis (bowel inflammation):** severe diarrhea (bloody or watery) with or without stomach cramps and fever			**√**
RARE **Severe allergic reaction:** with symptoms such as swollen mouth, throat, lips, difficulty breathing, skin reactions (rash, blisters, hives)			**√**
Liver problems: nausea, vomiting, abdominal pain and discomfort, yellowing of the skin and eyes		**√**	
Abnormal heart rhythm: Irregularities of the heartbeat (palpitations)			**√**
Severe skin reactions: like Stevens-Johnson syndrome and toxic epidermal necrolysis with symptoms such as severe rash, blistering or peeling skin. This may be associated with a high fever.			**√**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature 15°C to 30°C. Protect from light.

Keep out of reach and sight of children.

If you want more information about ERYC:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://www.pfizer.ca/, or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC.

Last Revised April 21, 2022