SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Erythromycin 250mg Gastro-resistant Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250mg of erythromycin.

Excipients: Erythromycin 250 mg capsules contain 25.6 mg of Lactose per capsule

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant capsule, hard.

Hard gelatin capsule with opaque orange cap and clear orange body, imprinted with "Erymax 250mg", and containing white enteric coated pellets of erythromycin base.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Erythromycin is an antibiotic effective in the treatment of bacterial disease caused by susceptible organisms.

Examples of its use are in the treatment of upper and lower respiratory tract infections of mild to moderate severity; skin and soft tissue infections including pustular acne.

Erythromycin is usually active against the following organisms in vitro and in clinical infection: Streptococcus pyogenes; Alpha haemolytic streptococci; Staphylococcus aureus; Streptococcus pneumoniae; Mycoplasma pneumoniae; Treponema pallidum; Corynebacterium diphtheriae; Corynebacterium minutissimum; Entamoeba histolytica; Listeria monocytogenes; Neisseria gonorrhoeae; Bordetella pertussis; Legionella pneumophila; Haemophilus influenzae; Chlamydia trachomatis; Propionibacterium acnes.

4.2 Posology and method of administration

Posology

Adults and elderly

250 mg every six hours - before or with meals. 500 mg every twelve hours may be given if desired; b.i.d. dosage should not be used if dosage exceeds one gram.

Children

The usual dose is 30-50 mg/kg/day erythromycin, in divided doses given twice daily or every six hours. In severe infections, this dose may be doubled; elevated doses should be given every six hours. The drug should be given before or with meals.

Note: Erythromycin Capsules may be given to children of any age who can swallow the capsules whole.

The capsules should be swallowed whole either before or with food; they should not be chewed.

Streptococcal Infections:

For active infection - a full therapeutic dose is given for at least ten days.

For continuous prophylaxis against recurrences of streptococcal infections in patients with evidence of rheumatic fever or heart disease, the dose is 250 mg b.i.d.

For the prevention of bacterial endocarditis in patients with valvular disease scheduled for dental or surgical procedures of the upper respiratory tract, the adult dose is 1 gram (children 20 mg/kg) 2 hours before surgery. Following surgery, the dose is 500 mg for adults (children 10mg/kg) orally every six hours for 8 doses.

Primary Syphilis: 30-40 grams given in divided doses over a period of 10-15 days.

Intestinal Amoebiasis: 250 mg four times daily for 10 to 14 days for adults: 30 to 50 mg/kg/day in divided doses for 10 to 14 days for children.

Legionnaires' Disease: 1-4 g daily until clinical signs and symptoms indicate a clinical cure. Treatment may be prolonged.

Pertussis: 30-50 mg/kg/day given in divided doses for 5 - 14 days, depending upon eradication of a positive culture.

Acne: initially, 250 mg twice daily, which may be reduced to a maintenance dose of 250 mg once daily after one month according to response.

Method of administration: Oral use

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Erythromycin is contraindicated in patients taking simvastatin, tolterodine, mizolastine, amisulpride, astemizole, terfenadine, domperidone, cisapride, pimozide, ergotamine, dihydroergotamine, or sertindole.

4.4 Special warnings and precautions for use

Erythromycin is excreted principally by the liver, so caution should be exercised in administering the antibiotic to patients with impaired hepatic function or concomitantly receiving potentially hepatotoxic agents. Hepatic dysfunction including increased liver enzymes and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported in patients taking erythromycin. Extended administration requires regular evaluation particularly of liver function. Therapy should be discontinued if significant hepatic dysfunction occurs.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening (see section 4.8). Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including erythromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of C. difficile. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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 (See sections 4.3 & 4.5).

There have been reports suggesting erythromycin does not reach the foetus in adequate concentrations to prevent congenital syphilis. Infants born to women treated during pregnancy with oral erythromycin for early syphilis should be treated with an appropriate penicillin regimen.

It has been reported that erythromycin may aggravate the weakness of patients with myasthenia gravis.

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

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients with concomitant use of erythromycin and HMG-CoA reductase inhibitors (see sections 4.3 and 4.5).

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 (see sections 4.3 and 4.5).

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Prolonged use of erythromycin has caused overgrowth of non-susceptible bacteria or fungi; this is a rare occurrence.

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. In one cohort of 157 newborns who were given erythromycin for pertussis prophylaxis, seven neonates (5%) developed symptoms of non-bilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy. 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.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 interactions:
Concomitant use of erythromycin with certain drugs metabolised by the cytochrome P450 system is likely to result in an increased frequency or seriousness of adverse effects associated with these drugs. The concomitant use of erythromycin with mizolastine, amisulpride, astemizole, cisapride, pimozide, sertindole and terfenadine is contraindicated due to the risk of QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsades de pointes. The concomitant use of erythromycin with ergotamine and dihydroergotamine is contraindicated due to the risk of ergot toxicity. Concomitant use with simvastatin is contraindicated due to the risk of myopathy and rhabdomyolysis whilst concomitant use with tolterodine is contraindicated due to increased risk of overdose.

Other drugs metabolised by the cytochrome P450 system, such as acenocoumarol, atorvastatin, bromocriptine, buspirone, cabergoline, carbamazepine, ciclosporin, cilostazol, clozapine, digoxin, disopyramide, eletriptan, felodipine, hexobarbital, methylprednisolone, midazolam, omeprazole, phenytoin, quetiapine, quinidine, rifabutin, sildenafil, tacrolimus, tadalafil, theophylline, triazolobenzodiazepines (e.g. triazolam, alprazolam) and releated benzodiazepines, valproate, vinblastine, antifungals e.g. fluconazole, ketoconazole and itraconazole, warfarin and zopiclone, may be associated with elevated serum levels if administered concomitantly with erythromycin. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant 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. Because of the risk of toxicity, appropriate monitoring should be undertaken, and dosage should be adjusted as necessary. Particular care should be taken with medications known to prolong the QTc interval of the electrocardiogram.

Oral anticoagulants: there have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants (e.g.warfarin) are used concomitantly.

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.

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.

Antihistamine H1 antagonists: care should be taken in the coadministration of erythromycin with H1 antagonists such as terfenadine, astemizole and mizolastine due to the alteration of their metabolism by erythromycin.

Other interactions:
HMG-CoA Reductase Inhibitors: erythromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g. lovastatin and simvastatin). Patients receiving concomitant lovastatin and erythromycin should be carefully monitored as cases of rhabdomyolysis have been reported in seriously ill patients. Rhabdomyolysis has also been reported with concomitant simvastatin and erythromycin, and caution is therefore recommended when erythromycin is used concurrently with other HMG-CoA reductase inhibitors. It is recommended that therapy with simvastatin is suspended during the course of treatment.

When oral erythromycin is given concurrently with theophylline, there is also a significant decrease in erythromycin serum concentrations, which could result in subtherapeutic concentrations of erythromycin.

Anti-bacterial agents: an *in vitro* antagonism exists between erythromycin and the bactericidal beta-lactam antibiotics (e.g. penicillin, cephalosporin). Erythromycin should be used with caution if administered concomitantly with lincomycin, clindamycin or chloramphenicol, as competitive inhibition may occur. The same applies for streptomycin, tetracyclines and colistin.

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

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

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

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.

An increased plasma concentration of erythromycin has been reported with concomitant cimetidine treatment, leading to increased risk of toxicity, including reversible deafness.

4.6 Fertility, pregnancy and lactation

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.

Like all drugs erythromycin should be used in pregnancy only when clearly indicated. Erythromycin crosses the placental barrier.

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

Nursing mothers: erythromycin is excreted in human milk and should be used in lactating women only if clearly needed.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Blood and lymphatic system disorders
Eosinophilia

Cardiac disorders
QTc interval prolongation, torsades de pointes, palpitations, cardiac arrhythmias have been reported rarely in patients receiving erythromycin.

Ear and labyrinth disorders
Tinnitus, deafness

Transient hearing disturbances and deafness have been reported with doses of erythromycin usually greater than 4g daily, and usually given intravenously.

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:
anorexia, infantile hypertrophic pyloric stenosis.

Nausea and abdominal discomfort can occur at elevated doses; diarrhoea and vomiting are less common.

Pancreatitis has been reported rarely.

Superinfections including pseudomembranous colitis have been occasionally reported to occur in association with erythromycin therapy.

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

Hepatobiliary disorders
Cholestatic hepatitis, hepatomegaly, hepatic failure, hepatocellular hepatitis (see section 4.4).

Hepatotoxicity: There have been reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving erythromycin products and due to combined cholestatic and hepatocellular injury although less commonly than with erythromycin estolate. Abnormal liver function tests may occur.

Immune system disorders
There have been rare reports of skin rashes, including pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Serious allergic reaction, including anaphylaxis, has been reported.

Investigations
Increased liver enzyme values.

Nervous system disorders
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.

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, acute generalised exanthematous pustulosis (AGEP)

Vascular disorders
Hypotension.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms
Severe nausea, vomiting, diarrhoea and hearing loss have been reported.

Treatment
Gastric lavage and general supportive therapy. Erythromycin is not removed by peritoneal dialysis or haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use. ATC code: J01FA01.

Erythromycin base and its salts are readily absorbed in the microbiologically active form. Erythromycin is largely bound to plasma proteins and after absorption erythromycin diffuses readily into most body fluids.

Erythromycin acts by inhibition of protein synthesis by binding 50s ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis.

5.2 Pharmacokinetic properties

After administration of a single dose of erythromycin 250 mg, peak serum levels are attained in approximately 3 hours.

In the presence of normal hepatic function, erythromycin is concentrated in the liver and is excreted in the bile. After oral administration, less than 5% of the administered dose can be recovered in the active form in the urine.

5.3 Preclinical safety data

Pre-clinical safety data does not add anything of further significance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose acetate phthalate, lactose, potassium phosphate monobasic, povidone, diethyl phthalate, purified water, sunset yellow, titanium dioxide, gelatin, erythrosine, quinoline yellow.

The printing ink contains:
Black iron oxide (E172), shellac, potassium hydroxide and propylene glycol.

6.2 Incompatibilities

None known.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package. Protect from moisture and light.

6.5 Nature and contents of container

PVdC/ PVC/ Aluminium Blister packs containing 4, 8, 28, 30, 100, 112 capsules.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Cephalon UK Limited
Ridings Point
Whistler Drive
Castleford
West Yorkshire
WF10 5HX
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16260/0024

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