SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Erythromycin 250 mg Gastro-resistant Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Erythromycin 250mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet

Reddish orange coloured round biconvex tablets, plain on both sides. They are made gastro-resistant by enteric coating.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the prophylaxis and treatment of infections caused by Erythromycin sensitive organisms.

Erythromycin is highly effective in the treatment of a great variety of clinical infections such as:

1. Upper respiratory tract infections: Tonsillitis, peritonsillar abscess, pharyngitis, laryngitis, sinusitis, secondary infections in influenza and common colds.

2. Lower respiratory tract infections: Tracheitis, acute and chronic bronchitis, pneumonia (lobar pneumonia, bronchopneumonia, primary atypical pneumonia), bronchiectasis, Legionnaire's disease

3. Ear infections: Otitis media and otitis externa, mastoiditis.

4. Eye infections: Blepharitis

5. Oral infections: Gingivitis, Vincent's angina

6. Skin and soft tissue infections: Boils and carbuncles, paronychia, abscesses, pustular acne, impetigo, cellulitis, erysipelas

7. Gastro-intestinal infections: cholecystitis, staphylococcal enterocolitis

8. Prophylaxis: pre- and post- operative trauma, burns, rheumatic fever

9. Other infections: osteomyelitis, urethritis, gonorrhoea, syphilis, lymphogranuloma venereum, diphtheria, prostatitis, scarlet fever

4.2 Posology and method of administration

Posology

For oral use administration

Adults and children over 8 years: For mild to moderate infections 2g daily in divided doses. Up to 4g daily in severe infections.

Elderly: No special dosage recommendations.

Note: For younger children, infants and babies, Erythromycin suspensions, are normally recommended. The recommended dose for children age 2-8 years, for mild to moderate infections, is 1 gram daily in divided doses. The recommended dose for infants and babies, for mild to moderate infections, is 500 mg daily in divided doses. For severe infections doses may be doubled.

Method of administration

Swallow whole with a glass of water. Do not crush or chew.

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 or pimozide.

Erythromycin is contraindicated with ergotamine and dihydroergotamine.

Erythromycin should not be given to patients with a history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (see section 4.4 and 4.5)
Erythromycin should not be given to patients with electrolyte disturbances (hypokalaemia, hypomagnesaemia due to the risk of prolongation of QT interval).

4.4 Special warnings and precautions for use

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

Erythromycin 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 with erythromycin.

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.

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.

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

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

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

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. Epidemiological studies including data from meta-analyses suggest a 2-3-fold increase in the risk of IHPS following exposure to erythromycin in infancy. This risk is highest following exposure to erythromycin during the first 14 days of life. Available data suggests a risk of 2.6% (95% CI: 1.5 -4.2%) following exposure to erythromycin during this time period. The risk of IHPS in the general population is 0.1-0.2%. Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or chlamydia), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Parents should be informed to contact their physician if vomiting or irritability with feeding occurs.

Cardiovascular Events

Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in patients treated with macrolides including erythromycin (see sections 4.3, 4.5 and 4.8). Fatalities have been reported.

Erythromycin should be used with caution in the following;
Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia. Patients concomitantly taking other medicinal products associated with QT prolongation (see section 4.3 and 4.5). Elderly patients may be more susceptible to drug- associated effects on the QT interval (see section 4.8).

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including erythromycin. Consideration of these findings should be balanced with treatment benefits when prescribing erythromycin.

4.5 Interaction with other medicinal products and other forms of interaction

Increases in serum concentrations of the following drugs metabolised by the cytochrome P450 system may occur when administered concurrently with erythromycin: acenocoumarol, alfentanil, astemizole, bromocriptine, carbamazepine, cilostazol, cyclosporin, digoxin, dihydroergotamine, disopyramide, ergotamine, hexobarbitone, methylprednisolone, midazolam, omeprazole, phenytoin, quinidine, rifabutin, sildenafil, tacrolimus, terfenadine, domperidone, theophylline, triazolam, valproate, vinblastine, and antifungals e.g fluconazole, ketoconazole and itraconazole. 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.

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.

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

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.

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

Anti-bacterial agents: an in vitro antagonism exists between erythromycin and the bactericidal beta-lactam antibiotics (e.g. penicillin, cephalosporin). Erythromycin antagonises the action of clindamycin, lincomycin and chloramphenicol. 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.

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

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

Post-marketing reports indicate that co-administration of erythromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm and ischaemia of the central nervous system, extremities and other tissues (see section 4.3).

Elevated cisapride levels have been reported in patients receiving erythromycin and cisapride concomitantly. This may result in QTc prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar effects have been observed with concomitant administration of pimozide and clarithromycin, another macrolide antibiotic.

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

erythromycin is given concurrently with theophylline there is a significant decrease in erythromycin serum concentrations. This decrease could result in sub-therapeutic concentrations of erythromycin.

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.

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

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

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.

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

There have been reports that maternal macrolide antibiotics exposure within 7 weeks of delivery may be associated with a higher risk of infantile hypertrophic pyloric stenosis (IHPS).

Erythromycin is excreted in breast milk. Caution should be exercised when administering erythromycin to lactating mothers due reports of infantile hypertrophic pyloric stenosis in breast-fed infants.

4.7 Effects on ability to drive and use machines

None reported

4.8 Undesirable effects

Blood and lymphatic system disorders:

Eosinophilia.

Cardiac disorders

QTc interval prolongation, torsades de pointes, palpitations and cardiac rhythm disorders including ventricular tachyarrhythmias, cardiac arrest, ventricular fibrillation (frequency not known).

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 disfunction, 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 and vertigo; however, a cause and effect relationship has not been established.

Psychiatric disorders

Hallucinations

Eye disorders

Mitochondrial Optic Neuropathy

Renal and urinary disorders

Interstitial nephritis

Skin and subcutaneous tissue disorders

Skin eruptions, prurituls, urticaria, exanthema, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.

Not Known: 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 Yellow Card Scheme at Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms: hearing loss, severe nausea, vomiting and diarrhoea.

Treatment: gastric lavage, general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Macrolides, ATC Code: J01FA01

Erythromycin exerts its antimicrobial action by binding to the 50S ribosomal sub-unit of susceptible microorganisms and suppresses protein synthesis. Erythromycin is usually active against most strains of the following organisms both in vitro and in clinical infections:

Gram-positive bacteria - *Listeria monocytogenes, Corynebacterium diphtheriae* (as an adjunct to antitoxin), Staphylococci *spp*, Streptococci *spp* (including Enterococci).

Gram-negative bacteria - *Haemophilus influenzae, Neisseria meningitidis, Neisseria gonorrhoeae, Legionella pneumophila, Moraxella (Branhamella) catarrhalis, Bordetella pertussis,* Campylobacter *spp*.

Mycoplasma - *Mycoplasma pneumoniae, Ureaplasma urealyticum.*

Other organisms - *Treponema pallidum*, Chlamydia spp, Clostridia spp, Lforms, the agents causing trachoma and lymphogranuloma venereum.

Note: The majority of strains of *Haemophilus influenzae* are susceptible to the concentrations reached after ordinary doses.

5.2 Pharmacokinetic properties

Peak blood levels normally occur within one hour of dosing of erythromycin ethylsuccinate granules. The elimination half life is approximately two hours. Doses may be administered two, three or four times a day.

Erythromycin ethylsuccinate is less susceptible than erythromycin to the adverse effect of gastric acid. It is absorbed from the small intestine. It is widely distributed throughout body tissues. Little metabolism occurs and only about 5% is eliminated in the urine. It is excreted principally by the liver.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch
Croscarmellose Sodium Type A
Povidone
Talc
Magnesium Stearate (E572)

Sub coat:
Hypromellose (E464)
Macrogol 6000
Erythrosine (E127)
Talc

Enteric coat:
Methacrylic Acid ethylacrylate Copolymer (1:1) dispersion 30%
Macrogol 6000
Talc
Polysorbate 80 (E433)
Erythrosine (E127)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

(a) Tablet container: 24 months.

(b) Blister: 30 months

6.4 Special precautions for storage

Do not store above 25^0C.
(a) Tablet container: Keep the container tightly closed. Store in the original container.
(b) Blister: Store in the original package.

6.5 Nature and contents of container

Tablet container
Nature: Polypropylene tamper evident tablet container with polyethylene cap.
Contents: 500 tablets

Blister:
Nature: 250 µm PVC/20 µm aluminium blister packs
Contents: 28 tablets.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Brown & Burk UK Limited
5 Marryat Close
Hounslow West
Middlesex
TW4 5DQ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 25298/0036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/11/2010

10. DATE OF REVISION OF THE TEXT

12/12/2019