SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Erythromycin Tablets BP 250mg
Rommix 250mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Erythromycin 250mg

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Gastro-resistant tablets

Reddish-orange opaque film coated round tablet

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 respiratory tract infections: Laryngitis, pharyngitis, sinusitis, secondary infections in colds and influenza, tonsillitis, peritonsillar abscess

Lower respiratory tract infections: Acute and chronic bronchitis, tracheitis, pneumonia, bronchiectasis, legionnaires disease

Eye infections: Blepharitis

Ear infections: Otitis media and otitis externa, mastoiditis

Oral infection: Gingivitis, Vincent's angina

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

Gastro-intestinal infections: Staphylococcal enterocolitis, cholecysitis

Other infections: Gonorrhoea, syphilis, urethritis, osteomyelitis, lymphogranuloma venereum, diptheria, prostatitis, scarlet fever

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

Consideration should be given to national and/or local guidance on the appropriate use of antibacterial agents

4.2 Posology and method of administration

Oral use

Adults and elderly
The usual dose is 250mg every six hours, taken one hour before meals. 500 mg every twelve hours may be given if desired. Twice daily dosing schedules should not be used if the total daily dose exceeds one gram. For severe infections up to 4g daily may be given in divided doses.

Children
Age, weight and severity of the infection are important factors in determining the correct dose. The usual dose is 30 – 50 mg/kg/day in divided doses given twice daily, or every six hours, one hour before meals. In severe infections, this dosage may be doubled; higher doses should be given every six hours.

4.3 Contraindications

Use in patients hypersensitive to erythromycin or any of the excipients.

Erythromycin is contraindicated in patients taking drugs known to prolong the QT interval due to the increased risk of cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsade de pointes (e.g. astemizole, terfenadine, , cisapride, pimozide etc; see also section 4.5).

Erythromycin is also contraindicated in patients taking drugs metabolised via cytochrome P450 3A4 in whom increased drug levels may lead to an increase in the frequency or severity of adverse events (e.g. ergotamine and dihydroergotamine, see also section 4.5).

4.4 Special warnings and precautions for use

Extended administration requires regular evaluation particularly of liver function. Therapy should be discontinued if significant hepatic dysfunction occurs.
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.

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

It has been reported that erythromycin may aggravate muscle weakness in patients with myasthenia gravis.

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.

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.

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.

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

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, 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) 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 Pregnancy and lactation

Pregnancy

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.

Lactation

Erythromycin is excreted in breast milk, therefore, caution should be exercised when erythromycin is administered to a nursing mother.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Modern clinical data required to determine the frequency of undesirable effects are lacking for erythromycin. Side effects associated with erythromycin therapy are usually mild. The most frequent side effects are gastrointestinal and are dose-related. There have been reports of serious allergic reactions, including anaphylaxis.

Blood and lymphatic system disorders: Eosinophilia

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

Investigations: Increased liver enzyme values

Psychiatric disorders: Hallucinations

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.

Ear and labyrinth disorders: Transient hearing disturbances, tinnitus and deafness (usually occurring at doses greater than 4 g daily) . There have been isolated reports of reversible hearing loss occurring chiefly with renal insufficiency or high doses.

Cardiac disorders: Cardiac rhythm disorders including ventricular tachyarrhythmias, QTc interval prolongation and torsades de pointes, palpitations.

Gastrointestinal disorders: The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. The following have been reported: Nausea, upper abdominal discomfort, diarrhoea, vomiting, pancreatitis, anorexia and 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: Jaundice (cholestatic/hepatocellular), cholestatic hepatitis, hepatitis, hepatic dysfunction, hepatomegaly, hepatic failure, abnormal liver function test values and hepatocellular hepatitis (see section 4.4).

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

Not known (frequency cannot be estimated from the available data): acute generalised exanthematous pustulosis (AGEP)

Renal and urinary disorders: Interstitial nephritis

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 Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

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

Treatment
General supportive measures should be employed. Consider gastric lavage only if the patient presents within one hour of ingesting a life-threatening amount of erythromycin.
Erythromycin is not removed by peritoneal dialysis or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Erythromycin is a macrolide antibiotic it is active against a wide variety of pathogenic organisms, gram-positive cocci-pneumococci, staphylococci and streptococci (including enterococci) – meningococci, mycoplasma, 1-forms, haemophilus influenzae (majority of

strains are susceptible to the concentrations reached after normal doses). Agents causing trachoma and lymphogranuloma venereum, clostridia, chlamydia, corynebacterium diptheriae (as adjunct to antitoxin), bordetella, neisseria, treponema pallidium. Erythromycin exerts its antimicrobial action by binding to the 50S ribosomal sub-unit of susceptible microorganisms and suppresses protein synthesis.

5.2 Pharmacokinetic properties

Tmax:	4 hours
Cmax:	0.3 - 0.5µg/ml
Vd:	0.78 ± 0.441/kg
T½:	1.6 ± 0.7 hours
Clearance:	9.1 – 4.1ml/min/kg

5.3 Preclinical safety data

Oral hamster:	LD_{50} 3018mg/kg.	Behavioural; lungs, thorax or respiration
Oral mouse:	LD_{50} 3112mg/kg.	No toxic effects noted
Oral rat:	LD_{50} 9272mg/kg.	No toxic effects noted

(Registry of toxic effects of chemical substances 1985-6)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Croscarmellose sodium type A
Povidone
Talc
Magnesium stearate

Sub coat:
Hydroxypropyl methylcellulose
Polyethylene glycol 6000
Dispersed red 18152 (E110 and E124)

Enteric coat:
Methacrylic acid copolymer
Polyethylene glycol 6000
Talc
Polysorbate 80
Dispersed red 18152 (E110 and E124)

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Protect from light, store in a dry place below 25°C

6.5 Nature and contents of container

Tablet container (securitainer) with polyethylene tamper evident seals
Pack sizes: 21, 100, 200, 500 and 1000 tablets

Blister strips composed of 250µm PVC and 20µm Al
Pack sizes: 28, 56, 84 and 100 tablets

6.6 Special precautions for disposal

Not applicable

7. MARKETING AUTHORISATION HOLDER

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Hertfordshire
WD18 9SS
Trading as: Co-pharma

8. MARKETING AUTHORISATION NUMBER(S)

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04/12/2017