ERYTHROMYCIN 250 MG CAPSULES

PL 10622/0148

UKPAR

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PL 10622/0148

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted PLIVA Pharma Ltd a Marketing Authorisation (licence) for the medicinal product Erythromycin 250 mg Capsules (Product Licence number: 10622/0148). This product is only available on prescription.

Erythromycin belongs to a class of drugs known as the macrolide antibiotics, which act by preventing the growth or multiplication of bacteria by interfering with their protein synthesis.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Erythromycin 250 mg Capsules outweigh the risks, hence a Marketing Authorisation has been granted.

ERYTHROMYCIN 250 MG CAPSULES

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Erythromycin 250 mg Capsules (PL 10622/0148) to PLIVA Pharma Ltd on 16 August 2007. This product is a Prescription Only Medicine (POM).

This application for capsules containing 250 mg of erythromycin base was submitted as an 'informed consent' application according to Article 10c of EC Directive 2001/83. The reference product is Hicyn 250 mg (PL 06934/0058) licensed to Ethypharm SA on 21 April 2006. This licence was a change of ownership from PL 05205/0009, granted 8 August 1994 to Laboratoires Prographarm.

PLIVA Pharma Ltd have confirmed that they have access to the relevant product data and that they are in possession of sufficient documentation to support the application**.** The reference product manufacturer (Ethypharm SA) has also confirmed willingness to manufacture for the applicant and a suitable letter of access has been provided. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report (PAR) was generated for it.

PHARMACEUTICAL ASSESSMENT REPORT

ACTIVE SUBSTANCE

A suitable Ph. Eur. Certificate of Suitability for the active substance, erythromycin, has been provided.

DRUG PRODUCT

The other ingredients of this medicine consist of pharmaceutical excipients, namely hydroxypropyl methylcellulose; methacrylic acid and ethyl acrylate copolymer; triacetin; neutral microgranules; talc; water and gelatine.

The product particulars are identical to that of the reference product regarding packs sizes; manufacturers of active ingredient and finished products; shelf life; storage; and the finished product specifications. These are all satisfactory.

Expert report
Expert statements regarding the chemical and pharmaceutical and toxico-pharmacological and clinical documentation have been provided and are satisfactory.

Summary of Product Characteristics (SPC)
The SPC is consistent with that of the reference product and is satisfactory.

Patient Information Leaflet (PIL)
The PIL for this product is satisfactory.

Labelling
All labelling for this product is satisfactory.

Discussion
This is a simple Marketing Authorisation application for a product that is identical to the reference product.

Conclusions
A Marketing Authorisation may be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for an application of this type.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The quality data for this application is consistent with that previously assessed for the cross-reference product and, as such, has been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY AND SAFETY

Erythromycin is a well known medicine and has been used as an antibiotic for many years. This application is identical to the approved Marketing Authorisation for Hicyn 250 mg (PL 06934/0058).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product and, as such, can be used interchangeably. Extensive clinical experience with erythromycin is considered to have demonstrated the therapeutic value of the compound. The risk benefit ratio is considered to be positive.

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 23 October 2003
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 15 June 2004
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 27 September 2004
4	The applicant responded to the MHRA's requests, providing further information on 19 May 2005
5	Following assessment of the response the MHRA requested further information relating to the quality dossier on 30 August 2005
6	The applicant responded to the MHRA's requests, providing further information on 6 December 2005
7	Following assessment of the response the MHRA requested further information relating to the quality dossier on 8 February 2006
8	The applicant responded to the MHRA's requests, providing further information on 3 December 2006
9	Following assessment of the response the MHRA requested further information relating to the quality dossier on 6 December 2006
10	The applicant responded to the MHRA's request, providing further information on 6 January 2007
11	Following assessment of the application the MHRA requested further information relating to the quality dossier 12 March 2007
12	The applicant responded to the MHRA's requests, providing further information on 16 May 2007
13	The application was determined on 16 August 2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Erythromycin 250mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250mg erythromycin base.
See Section 6.1 for excipients.

3 PHARMACEUTICAL FORM

Hard capsule containing enteric coated microgranules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

These are based on the antibacterial activity and pharmacokinetic characteristics of erythromycin. They take account of both the clinical studies carried out with this medicine and its place in the range of antibacterial products on the market.

Its use is limited to infections caused by the germs listed below as susceptible, notably in the following manifestations:
ENT, stomatological
Bronchopulmonary
Cutaneous (it should be noted that numerous strains of staphylococcus are resistant)
Osteoarticular
Urogenital (in particular those due to chlamydia trachomatis and ureaplasma urealyticum)
The chemoprophylaxis of acute articular rheumatism relapse in the case of contraindication to penicillin G or V.

4.2 Posology and method of administration

For oral use.

Adults:
250mg every 6 hours or 500mg every 12 hours.
When justified by the severity of the infection the dosage can be augmented by increasing the number of administrations (500mg three to four times a day). Thus, for pulmonary infections with mycoplasma pneumoniae of legionella, for chlamydia infections, and for other severe infections, the dosage regimen would be 500mg every 6 to 8 hours.

Acne:
Initially 1 twice daily reducing to maintenance of 1 once daily after one month.

Children:
30 to 50mg/kg/day in divided doses given every six hours, or twice daily.

4.3 Contraindications

Allergy to erythromycin.
Association with the vasoconstrictor ergot alkaloids, notably ergotamine and dihydroergotamine (see Section 4.5, Interactions with other medicinal products and other forms of interaction).
Severe liver insufficiency.
Migraine crisis treated with ergot derivatives (see Section 4.5, Interactions with other medicinal products and other forms of interaction).
Association with astemizole and terfenadine (see Section 4.5, Interactions with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

In cases of impaired hepatic insufficiency, the administration of erythromycin is not recommended. If it is necessary, then regular supervision with hepatic tests and eventually a reduced dosage regimen is justified.

Prolonged or repeated administration of erythromycin could favour the growth of non-susceptible organisms or the appearance of mycoses.

Asthmatic subjects treated with theophyllin should be subjected to special control for clinical symptoms of intoxication and eventually to drug monitoring for plasma concentrations of theophyllin (see Section 4.5, Interactions with other medicinal products and other forms of interaction).

Hepatic dysfunction including increased liver enzymes and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with erythromycin.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltose insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Ergotism manifestations with the possibility of necrosis of the extremities has been reported after the simultaneous use of erythromycin and products with ergotamine or other vasoconstrictor ergot derivatives. Such associations are contraindicated.

Astemizole, terfenadine: risk of ventricular rhythm disorders, notably ‘torsades de pointe’: reduction of astemizole liver metabolism by erythromycin. Such associations are contraindicated.
Combination with theophyllin should be avoided.

Combination with carbamazepine should be avoided.

In the case of combination with bromocriptin, it will be necessary to take into account the possible increase of bromocriptin plasma levels, with possible increase of anti-parkinsonian activity, or the appearance of overdose dopaminergic signs (dyskinesia).

Erythromycin increases circulating cyclosporin levels (inhibition of cyclosporin catabolism) and creatinine levels.

Combination with digoxin: *precaution of use*. Erythromycin can increase digoxin serum levels to toxic values. Clinical and electrocardiographic supervision are recommended together with eventual adaptation of the digoxin dosage regimen.

Combination with warfarin: *precaution of use*. Risk of haemorrhage. Increase of the anticoagulation effect of warfarin. Mechanism invoked: decrease of hepatic catabolism of warfarin. More frequent control of prothrombin level and adaptation of the dosage regimen of oral anticoagulant during treatment with macrolide and 8 days following its discontinuation.

The administration of an antibiotic so-called bacteriostatic like erythromycin, can counter the bactericidal effect of other antibiotics such as the beta-lactamines.

Erythromycin presents a microbiologic antagonism with lincomycin and clindamycin.

4.6 Pregnancy and lactation

Erythromycin should be used in pregnancy only when clearly indicated.

Erythromycin is found in the mother's milk at concentrations which can be superior to maternal serum concentrations, and can cause mild gastro-intestinal symptoms in breast-fed infants.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Digestive manifestations: nausea, vomiting, diarrhoea and gastralgia.
Transitory increases of transaminases and cholestatic hepatitis have been reported with erythromycin derivatives.
Very rare reversible auditive disturbances have been reported in particular with aged patients or patients with renal insufficiency, or with patients having received doses higher than 4g per day.

As with other broad spectrum antibiotics, pseudomembranous colitis has been reported rarely with erythromycin.

Reversible hearing loss associated with doses of erythromycin usually greater than 4g per day has been reported.

Allergic reactions are rare and mild, although anaphylaxis has occurred. Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis have rarely been reported.

Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur.

4.9 Overdose

Acute toxicity of erythromycin is weak. Overdosage symptoms are nausea, vomiting and diarrhoea. Recommended treatment: gastric lavage and/or administration of activated charcoal.

Neither haemodialysis nor peritoneal dialysis are capable of extracting erythromycin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Erythromycin is a macrolide antibiotic.

ATC code: J01F A01

The natural antibacterial spectrum of erythromycin is as follows:

Species Normally Susceptible	**MIC (µg/ml)**
Streptococcus pyogenes group A, beta haemolytic	0.005 – 0.2
Streptococcus sanguis	0.02 – 3.1
Bordetella pertussis	0.02 – 1.6
Corynebacterium diphteriae	0.006 – 3.1
Listeria monocytogenes	0.1 – 0.3
Clostridium perfringens	0.1 – 6
Mycoplasma pneumoniae	0.001 – 0.02
Chlamydia trachomatis	0.1 – 0.5
Legionella pneumophila	0.06 – 0.5
Treponema pallidum	-
Leptospira	-
Campylobacter jejuni	0.05 - > 50
Ureaplasma urealyticum	2 - > 4
Non-Constantly Susceptible Species	**MIC (µg/ml)**
Streptococcus pneumoniae (pneumococcus)	0.001 – 0.2
Neisseria menigitidis (menigococcus)	0.1 – 1.6
Neisseria gonorrhoeae (gonococcus)	0.005 – 0.4
Haemophilus influenzae	0.1 – 6
Bacteriodes fragilis	0.1 - > 100
Vibrio cholerae	-
Staphylococcus aureus	0.005 - > 100

Resistant Species	**MIC > 4 µg/ml**
Enterobacteriaceae	0.1>100
Pseudomonas	-

When constant strain susceptibility has not been established for a certain species, in vitro testing of the strain is the only method of establishing whether it is sensitive, intermediary or resistant.

Among the Streptococcus pyogenes of Group A few rare strains are resistant.

A microbiological antagonism exists between erythromycin, lincomycin and clindamycin.

Cross resistance is usual between the various macrolides.

Germs having a MIC <1 or possibly 2µg/ml are usually considered as susceptible. For germs with a MIC of 2 – 4 µg/ml the failure frequency increases depending on the site of infection.

5.2 Pharmacokinetic properties

Erythromycin 250mg capsules is a dosage from of erythromycin base presented as microgranules coated with a gastro-resistant film.
The pharmacokinetic parameters are as follows.

Absorption
In healthy subjects, with one administration of 2 capsules before meals, the concentration peak was attained at a mean of 2.9 hours, the apparent half-life of elimination was 1.9 hours, the mean maximum concentration being 2.47mg/l.

Distribution
Erythromycin diffuses well into the tissues of the organism, notably in the lungs, the tonsils and the prostate.
Erythromycin diffuses only lightly in the cerebrospinal fluid.
Erythromycin traverses the placental barrier. It becomes concentrated in milk.
Binding with plasma proteins: the binding of erythromycin base with plasma proteins is about 65%, with a predominance for alpha 1 acid glycoprotein (approximately 55%). (Study with erythromycin C 14).
Biotransformation
Erythromycin is partly metabolised by the liver.

Excretion
Erythromycin concentrates in the liver and is eliminated in its active form, principally by the bile, at concentrations superior to those of serum.
Renal elimination is in the order of 2 – 5% for the unchanged form.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Neutral microgranules (75% sucrose, 25% corn starch)

Hypromellose
Triacetin
Methacrylic acid and ethyl acrylate copolymer
Talc
Capsule (gelatin)

6.2 Incompatibilities

None.

6.3 Shelf life

24 Months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Cardboard boxes of 28 or 30 capsules containing enteric coated microgranules in doses of 250mg, in thermoformed PVC/aluminium blisters.
Dispensing only under medical prescription.

6.6 Special precautions for disposal

No specific requirements.

7 MARKETING AUTHORISATION HOLDER

PLIVA Pharma Ltd.
Vision House
Bedford Road
Petersfield
Hampshire, GU32 3QB

8 MARKETING AUTHORISATION NUMBER(S)

PL 10622/0148

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/08/2007

10 DATE OF REVISION OF THE TEXT

16/08/2007

PATIENT INFORMATION LEAFLET

Your prescription for Erythromycin 250mg Capsules

Please read this carefully before you start to use your capsules.

This leaflet contains important information about your treatment. If you have any doubts or questions, or you are not sure about anything, ask your doctor or pharmacist.

Keep this leaflet. You may need to read it again.

The name of your medicine is Erythromycin 250mg Capsules.

What is in the capsules?

Each Erythromycin 250mg Capsule contains 250mg of erythromycin. The other ingredients of Erythromycin 250mg Capsules are neutral micro-granules (containing sucrose and corn starch), hydroxypropyl methylcellulose, triacetin, methacrylic acid and ethyl acrylate copolymer, and talc. The capsule shell contains gelatine. Erythromycin 250mg Capsules are available in blister packs of 28 or 30 capsules, although not all pack sizes may be marketed.

What do the capsules do?

Erythromycin is an antibiotic, belonging to a class of drugs known as the macrolide antibiotics, which act by preventing the growth or multiplication of bacteria.

Who provides the capsules?

The manufacturer for Erythromycin 250mg Capsules is
Ethypharm, Z.I. Saint Arnoult, 28170 Châteauneuf-en-Thymerais, France.

The marketing authorisation holder is
PLIVA Pharma Ltd, Vision House, Bedford Road, Petersfield, Hampshire, GU32 3QB.

What are the capsules for?

This product has been prescribed for you personally and you should not pass it on to others.

This medicine is prescribed for infections due to germs that are susceptible to erythromycin, including the following types of infections:

- Infections of the ear, nose, throat and mouth.
- Infections of the bronchial tubes and the lungs (i.e. chest infections).
- Infections of the skin and tissues.
- Infections of the bones and joints.
- Infections of the urinary organs and genitalia (in particular those due to *chlamydia trachomatis* and ureplasma urealyticum).
- Prevention of acute joint rheumatism relapse, where penicillin is unsuitable.

Before using your capsules:

Ask yourself the following questions:

- Have you ever taken a medicine containing erythromycin before and had an unusual or allergic reaction?
- Are you allergic to any of the other ingredients listed above?
- Do you suffer from asthma and are you receiving theophylline?
- Are you suffering from severe liver problems?
- Do you suffer from migraine attacks which are treated with ergot derivatives?
- Are you pregnant or is there a chance you might be pregnant, or are you breast-feeding? **Only when clearly indicated by your doctor** should Erythromycin 250mg Capsules be used if you are a pregnant or breast-feeding mother.

If the answer to any of these questions is **yes**, tell your doctor or pharmacist as soon as possible and before taking any capsules.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Can you use Erythromycin 250mg Capsules with other medicines?

It is also important to check whether you are or have recently been taking other medicines before you start taking Erythromycin 250mg Capsules. In particular, if you have recently been or if you are currently taking any of the following drugs, you should not take Erythromycin 250mg Capsules until you have discussed this with your doctor. Tell your doctor or pharmacist as soon as possible and before taking any capsules:

Ergot alkaloids (e.g. Ergotamine, used in migraine), Astemizole and Terfenadine (anti-histamines used to relieve allergic reactions including hayfever and conjunctivitis), Theophylline (used in asthma), Carbamazepine (several uses including treatment of epilepsy, pain management and depression), Bromocriptine (used to treat hormone disorders linked with excess prolactin levels, acromegaly and Parkinson's disease), Digoxin (used in heart failure and irregular heart beats), Warfarin (used to thin the blood), Lincomycin and Clindamycin (used to treat some infections), Ciclosporin (used to suppress the immune system, and to treat dermatitis, psoriasis and severe rheumatoid arthritis), and some other antibiotics, such as the penicillins.

It is important that you inform and consult your doctor, pharmacist or nurse if you are taking, or have recently taken, any other medicine – even those not prescribed.

If you are not sure whether another medicine you are taking may be one of the types listed above, check with your doctor or pharmacist.

Taking your capsules:

It is important to take the capsules as directed by your doctor. Check the medicine label to see how many capsules to take and how often to take them. If you are not sure, ask your doctor or pharmacist.

Swallow the capsules whole with a drink of water. Do not chew the capsules. You should take the capsule just before or with meals. Take the complete course of capsules, as directed by your doctor.

Adults

The usual dose is 250mg (1 capsule) every 6 hours or 500mg (2 capsules) every 12 hours.

When justified by the severity of the infection your doctor may decide to increase the dose up to 500mg (2 capsules) every 6 to 8 hours.

Acne: initially 1 capsule two times a day, followed by 1 capsule a day after 1 month of treatment or when directed by your doctor.

Children

Your doctor will have worked out the dose according to the weight of the child.

If you forget to take a dose

If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose though, do not double the dose, just carry on as before.

If you take too many capsules

It is important to stick to the dose on the label of your medicine. If you or someone else swallow too many capsules all together, or you think a child has swallowed any of these capsules you should immediately contact your doctor or visit your nearest hospital emergency department. Always take with you any capsules left over and also the container as this will allow the medicine to be more easily identified.

Can your capsules have any side effects?

Like all medicines, Erythromycin 250mg Capsules can have side effects. The possible types of adverse effects are listed below.

If any of the following symptoms come on soon after taking these capsules, stop taking the capsules and tell your doctor immediately. This kind of reaction is extremely rare and may mean you are suffering from an allergic reaction to the capsules:

- difficulty in breathing
- swelling of the face and/or throat
- unexplained rash, itching, redness, blistering of the skin or any other skin trouble.

Other undesirable effects which may sometimes happen while taking Erythromycin 250mg Capsules include the following:

- Nausea, vomiting, stomach pains or diarrhoea.
- Hepatitis and liver problems may occur. This may show as yellowing of the skin and/or whites of the eyes, abdominal discomfort and loss of appetite.
- Temporary loss of hearing, particularly if you are taking a high dose of your medicine.
- A diarrhoeal disease (known as pseudomembranous colitis) may also occur. This may show as watery diarrhoea, fever and cramps.

If symptoms persist or become troublesome you should consult your doctor.

If anything else happens which is not mentioned in this leaflet, tell your doctor or pharmacist.

Storing your capsules:

This medicinal product does not require any special storage conditions.
Store your capsules in a safe place where children cannot reach them.

Do not use the capsules after the expiry date printed on the carton and the strip of capsules.
If you have any capsules which are out of date, return them to your pharmacist for disposal.

Keep your capsules in the pack in which they were given to you, do not transfer them to another container.

Further information:

Remember: this treatment is for YOU. Only a doctor can prescribe it for you. Never give it to others. It may harm them even if their symptoms are the same as yours.

Date of preparation: November 2006

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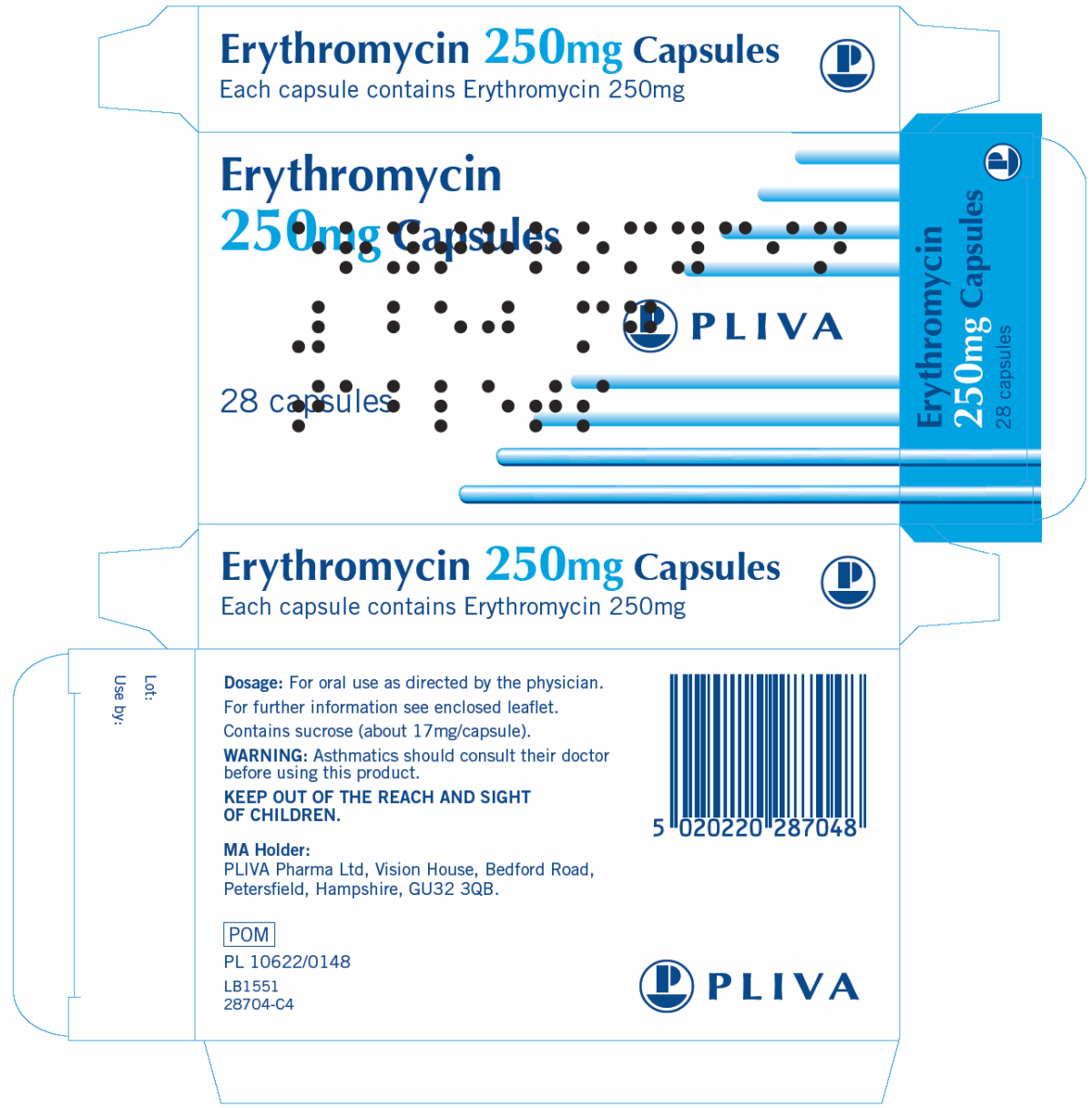
PLIVA

LABELLING

Carton:



Blister foil: