Erythromycin Ethylsuccinate 500 mg film-coated Tablets

(Erythromycin ethylsuccinate)

PL 30684/0229

UKPAR

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LAY SUMMARY

Erythromycin Ethylsuccinate 500 mg film-coated Tablets
(erythromycin ethylsuccinate, film-coated tablets, 500 mg)

This is a summary of the Public Assessment Report (PAR) for Erythromycin Ethylsuccinate 500 mg film-coated Tablets (PL 30684/0229). It explains how Erythromycin Ethylsuccinate 500 mg film-coated Tablets was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Erythromycin Ethylsuccinate 500 mg film-coated Tablets.

For practical information about using Erythromycin Ethylsuccinate 500 mg film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Erythromycin Ethylsuccinate 500 mg film-coated Tablets and what are they used for?
Erythromycin Ethylsuccinate 500 mg film-coated Tablets is a ‘generic medicine’. This means that Erythromycin Ethylsuccinate 500 mg film-coated Tablets are similar to a reference medicine already authorised in the European Union (EU) called Pantomicina 500 E.S (Amdipharm Limited, Spain). The equivalent reference medicine in the UK is called Erythroped A Tablets (Amdipharm UK Limited, UK). Both reference medicines can be considered as part of the same ‘global marketing authorisation (GLA)’ for this medicinal product.

Erythromycin Ethylsuccinate 500 mg film-coated Tablets contains the active substance erythromycin ethylsuccinate. Erythromycin Ethylsuccinate 500 mg film-coated Tablets are used to prevent and treat infections such as:
- Throat and sinus infections.
- Chest infections, such as bronchitis and pneumonia.
- Ear infections.
- Mouth infections.
- Eye infections.
- Skin and tissue infections, such as acne.
- Stomach and intestinal infections.
- Prevention of infection following burns or operations, other infections such as sexually transmitted diseases, bone infections or scarlet fever.

How do Erythromycin Ethylsuccinate 500 mg film-coated Tablets work?
Erythromycin Ethylsuccinate 500 mg film-coated Tablets contain the active ingredient erythromycin ethylsuccinate which belongs to a group of medicines called antibiotics. Erythromycin ethylsuccinate is a macrolide antibiotic which means it works by impeding the growth of bacteria in the body.

How are Erythromycin Ethylsuccinate 500 mg film-coated Tablets used?
Erythromycin Ethylsuccinate 500 mg film-coated Tablets can be obtained only with a prescription. The medicine should be taken exactly as advised by the doctor or pharmacist. The patient must check with their doctor or pharmacist if they are not sure.

The patient’s doctor will decide on how many tablets the patient should take. The dose will depend on the type of infection the patient has and where the infection is in their body. The length of treatment will depend on how serious the patient’s infection is.

If the patient feels that the effect of their medicine is too weak or strong, they must not change the dose themselves, but ask their doctor.
Erythromycin Ethylsuccinate 500 mg film-coated Tablets are taken by mouth.

Erythromycin Ethylsuccinate 500 mg film-coated Tablets should be swallowed whole with a drink of water. The tablets may be taken just before or with meals or food.

For further information on how Erythromycin Ethylsuccinate 500 mg film-coated Tablets are used, refer to the package leaflet and Summary of Product Characteristics available on the MHRA website.

What benefits of Erythromycin Ethylsuccinate 500 mg film-coated Tablets have been shown in studies?
As Erythromycin Ethylsuccinate 500 mg film-coated Tablets is a generic medicine; studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Pantomicina 500 E.S (Amdipharm Limited, Spain). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Erythromycin Ethylsuccinate 500 mg film-coated Tablets?
Because Erythromycin Ethylsuccinate 500 mg film-coated Tablets is a generic medicine and is bioequivalent to the reference medicine, the benefits and possible side effects are taken as being the same as those of the reference medicine.

For the full list of restrictions, see the package leaflet available on the MHRA website.

Why are Erythromycin Ethylsuccinate 500 mg film-coated Tablets approved?
It was concluded that, in accordance with EU requirements, Erythromycin Ethylsuccinate 500 mg film-coated Tablets have been shown to have comparable quality and to be bioequivalent Pantomicina 500 E.S (Amdipharm Limited, Spain). Therefore, the view was that, as for Pantomicina 500 E.S (Amdipharm Limited, Spain), the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Erythromycin Ethylsuccinate 500 mg film-coated Tablets?
A risk management plan has been developed to ensure that Erythromycin Ethylsuccinate 500 mg film-coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Erythromycin Ethylsuccinate 500 mg film-coated Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Erythromycin Ethylsuccinate 500 mg film-coated Tablets
A Marketing Authorisation was granted in the UK on 07 November 2014.

The full PAR for Erythromycin Ethylsuccinate 500 mg film-coated Tablets follows this summary.

For more information about treatment with Erythromycin Ethylsuccinate 500 mg film-coated Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2014.
Erythromycin Ethylsuccinate 500 mg film-coated Tablets

PL 30684/0229

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Dawa Limited a Marketing Authorisation for the medicinal product Erythromycin Ethylsuccinate 500 mg film-coated Tablets (PL 30684/0229). The product is a prescription-only medicine (POM) indicated in adults, adolescents and children over 8 years of age for treatment of the following infections:

- Upper respiratory tract infections: tonsillitis, peritonsillar abscess, pharyngitis, laryngitis, sinusitis, secondary infections in influenza and common colds
- Lower respiratory tract infections: tracheitis, acute and chronic bronchitis, pneumonia (lobar pneumonia, bronchopneumonia, primary atypical pneumonia), bronchiectasis, Legionnaire’s disease
- Ear infection: otitis media and otitis externa, mastoiditis
- Oral infections: gingivitis, Vincent’s angina
- Eye infections: blepharitis
- Skin and soft tissue infections: boils and carbuncles, paronychia, abscesses, pustular acne, impetigo, cellulitis, erysipelas
- Gastrointestinal infections: cholecystitis, staphylococcal enterocolitis
- Prophylaxis: pre- and post-operative trauma, burns, rheumatic fever,
- Other infections: osteomyelitis, urethritis, syphilis, lymphogranuloma, venereum, diphtheria, prostatitis, scarlet fever.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, cross-referring to Pantomicina 500 E.S licensed on 01 July 1987 to Amdipharm Limited, Spain. The equivalent reference medicine in the UK is called Erythroped A Tablets (PL 20074/0040; Amdipharm UK Limited, UK). Both reference medicines can be considered as part of the same ‘global marketing authorisation (GLA)’ for this medicinal product. This is acceptable.

The active ingredient, erythromycin is a macrolide antibiotic (pharmacotherapeutic group: erythromycin; ATC code: J01FA01) which acts by binding to the 50s ribosomal subunit of susceptible microorganisms and thus interfering with their protein synthesis. Nucleic acid synthesis is not affected.

Resistance mainly occurs via target site modification by an rRNA-methylating enzyme by Erm-type methyltransferases.

A bioequivalence study was submitted to support this application comparing the applicant’s test product Erythromycin Ethylsuccinate 500 mg film-coated Tablets with the reference product Pantomicina 500 E.S (Amdipharm Limited, Spain) under fasting conditions. The applicant has stated that the bioequivalence study was conducted in accordance with the ethical principles that have their origins in the “Declaration of Helsinki (Seoul 2008)” and in compliance with the requirements of “ICH Guidelines for Good Clinical Practices (E6) 1996”, “Schedule Y of Drugs and Cosmetics Act, 20th January 2005”, “ICMR Ethical Guidelines for Biomedical Research on Human Subjects 2006”, “CDSCO Guidelines for BA/BE Studies, March 2005”. No subject was enrolled in the study without obtaining written informed consent and subjects were under medical supervision throughout their stay in the clinical facility to ensure their safety and well-being.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on a product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.
No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Erythromycin Ethylsuccinate 500 mg film-coated Tablets outweigh the risks and a Marketing Authorisation was granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Erythromycin ethylsuccinate

Molecular formula: \(\text{C}_{43}\text{H}_{75}\text{NO}_{16}\)
Molecular weight: 862.05

Structure:

![Chemical structure of Erythromycin Ethylsuccinate]

Appearance: A white crystalline powder.
Solubility: Practically insoluble in water, freely soluble in acetone, ethanol and methanol.

Erythromycin ethylsuccinate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients:
Tablet core: pregelatinised starch, anhydrous calcium hydrogen phosphate, sodium starch glycolate, povidone and magnesium stearate.
Tablet coating: Opadry Yellow 03G52008 (consisting of hypromellose, titanium dioxide, macrogol, Quinoline Yellow Aluminium Lake and iron oxide yellow).
Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the tablet coating Opadry Yellow 03G520008 which complies with suitable in-house specifications.

Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the development programme was to formulate a safe efficacious, stable dosage form bioequivalent to the reference product Pantomicina 500 E.S (Amdipharm Limited, Spain).

Suitable pharmaceutical development data have been provided for this application.

Comparable impurity and *in-vitro* dissolution profiles have been provided for this product and the reference product.

**Manufacturing Process**

A satisfactory description of the manufacturing process and batch formulae for the drug product has been provided. The manufacturing process has been validated at pilot scale. The marketing authorisation holder (MAH) has committed to perform additional process validation on future commercial-scale batches.

**Control of Finished Product**

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided that complies with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**

The finished product is packed in polyvinyl chloride (PVC)/aluminium blisters. The blisters are packed with the Patient Information Leaflet in outer cartons in pack sizes of 10, 12, 14, 24, 28, 30, 56 and 84 film-coated tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability**

Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability studies on batches of finished product.
Bioequivalence
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA (Marketing Authorisation Application) Form
The MAA form is satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of erythromycin are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
As the product is intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of erythromycin is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or are required for this application.

Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:

STUDY
An open label, randomised, single dose, two-way crossover study to compare the pharmacokinetics of the applicant’s test product Erythromycin Ethylsuccinate 500 mg film-coated Tablets (Dawa Limited) versus the reference product, Pantomicina 500 E.S (Amdipharm Limited, Spain), in healthy adult male volunteers under fasting conditions.

The volunteers were administered a single dose (500 mg) of either the test or the reference product with 240 ml of water, after an overnight fast of at least 10 hours. Water was permitted ad lib until 1 hour before dosing and again 1 hour after dosing.

Blood samples were collected before and up to and including 12 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

Pharmacokinetic parameters (geometric least squares mean, ratios and confidence intervals [CI]) of erythromycin

<table>
<thead>
<tr>
<th></th>
<th>Test/Reference Ratio (%)</th>
<th>Intra CV (%)</th>
<th>90% Confidence interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/ml)</td>
<td>95.85</td>
<td>10.63</td>
<td>91.24-100.7</td>
</tr>
<tr>
<td>AUC_{0-t} (ng.h/ml)</td>
<td>102.92</td>
<td>19.14</td>
<td>94.23-112.42</td>
</tr>
<tr>
<td>AUC_{0-\infty} (ng.h/ml)</td>
<td>105.26</td>
<td>23.88</td>
<td>94.34-117.44</td>
</tr>
</tbody>
</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-\infty} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
90% geometric CI calculated from ln-transformed data
Test Erythromycin Ethylsuccinate 500 mg film-coated Tablets
Reference Pantomicina 500 E.S
Intra CV (%) Intra coefficient of variation

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC, and C_{max} values for erythromycin lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Pantomicina 500 E.S (Amdipharm Limited, Spain).
EFFICACY
The efficacy of erythromycin is well-known. No new efficacy data have been submitted and none are required for this type of application.

SAFETY
With the exception of the safety data generated during the bioequivalence study no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues were raised during the bioequivalence study.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

An acceptable Risk Management Plan has been provided. Routine risk minimisation is provided through the Summary of Product Characteristics and the Patient Information Leaflet and this is sufficient.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are acceptable from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in line with current guidance. The labelling is also in line with current guidance.

CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The quality characteristics of Erythromycin Ethylsuccinate 500 mg film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of erythromycin are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new clinical data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s product Erythromycin Ethylsuccinate 500 mg film-coated Tablets and the reference product Pantomicina 500 E.S (Amdipharm Limited, Spain).

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of erythromycin is well-known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the originator product are interchangeable. Extensive clinical experience with erythromycin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
Erythromycin Ethylsuccinate 500 mg film-coated Tablets

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STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation application on 27 March 2013.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 03 April 2013.
3. Following assessment of the application the MHRA requested further information relating to the dossier on 11 July 2013 and 13 February 2014.
4. The applicant responded to the MHRA’s requests, providing further information on the dossier on 11 July 2013 and 04 April 2014.
5. The application was granted on 07 November 2014.
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Each tablet contains 500mg of erythromycin (as Erythromycin Ethylsuccinate)

For oral use only. See enclosed leaflet for further information. Read the package leaflet before use. Keep out of the sight and reach of children.
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