



Medicines & Healthcare products  
Regulatory Agency



## **Public Assessment Report**

### **Decentralised Procedures**

**Clarithromycin 250 mg and 500 mg film-coated tablets**

**(clarithromycin)**

**Procedure No: UK/H/6183/001-2/DC**

**UK Licence Number: PL 42092/0001-0002**

**Nexcape Pharmaceuticals Ltd**

## **LAY SUMMARY**

### **Clarithromycin 250 mg and 500 mg film-coated tablets (clarithromycin)**

This is a summary of the Public Assessment Report (PAR) for Clarithromycin 250 mg and 500 mg film-coated tablets (PL 42092/0001-0002; UK/H/6183/001-02/DC). It explains how Clarithromycin 250 mg and 500 mg film-coated tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Clarithromycin 250mg and 500 mg film-coated tablets.

The products will be collectively referred to as Clarithromycin tablets throughout the remainder of this lay summary (PAR) for ease of reading.

For practical information about using Clarithromycin tablets, patients should read the package leaflet or contact their doctor or pharmacist.

#### **What are Clarithromycin tablets and what are they used for?**

Clarithromycin tablets are 'generic medicines'. This means that Clarithromycin tablets are similar to 'reference medicines' already authorised in the European Union (EU) called Klaricid 250 mg and 500 mg Tablets (Mylan Products Limited; PL 46302/0016-7).

Clarithromycin tablets are used in adults and children 12 years and older to treat infections such as:

- Bacterial pharyngitis
- Mild to moderate community acquired pneumonia
- Acute bacterial sinusitis (adequately diagnosed)
- Acute exacerbation of chronic bronchitis
- Skin infections and soft tissue infections of mild to moderate severity

Clarithromycin tablets are also used to treat *Helicobacter pylori* associated ulcers in adults (in appropriate combination with antibacterial therapeutic regimens and appropriate ulcer healing agent).

#### **How do Clarithromycin tablets work?**

Clarithromycin tablets contain the active ingredient clarithromycin, which belongs to a group of medicines called macrolide antibiotics. Antibiotics stop the growth of bacteria (bugs) which cause infections.

#### **How are Clarithromycin tablets used?**

Clarithromycin tablets are taken by mouth. Clarithromycin tablets should be taken with food and must be swallowed whole without chewing.

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient must check with their doctor or pharmacist if they are not sure.

The usual dose of Clarithromycin tablets for adults and children over 12 years is one 500 mg tablet once a day or two 250 mg tablets once a day for 6 to 14 days. A doctor may increase the dose to two 500 mg tablets daily in severe infections.

#### **For treating *Helicobacter pylori* infections associated with duodenal ulcers in adults:**

There are a number of effective treatment combinations available to treat *Helicobacter pylori* in which Clarithromycin tablets are taken together with one or two other drugs.

These combinations include the following and are usually taken for 6 to 14 days:

One Clarithromycin 500 mg tablet taken twice a day together with amoxicillin, 1000 mg taken twice a day plus lansoprazole, 30 mg twice a day.

One Clarithromycin 500 mg tablet taken twice a day together with metronidazole, 400 mg taken twice a day plus lansoprazole, 30 mg twice a day.

One Clarithromycin 500 mg tablet taken twice a day together with amoxicillin, 1000 mg taken twice a day or metronidazole, 400 mg taken twice a day plus omeprazole, 40 mg a day.

One Clarithromycin 500 mg tablet taken twice a day together with amoxicillin, 1000 mg taken twice a day plus omeprazole, 20 mg taken once a day.

One Clarithromycin 500 mg tablet taken three times a day together with omeprazole 40 mg taken once a day, for 7 days.

The treatment combination that patients receive may differ slightly from the above. The patient's doctor will decide which treatment combination is the most suitable. If patients are unsure which tablets to take or how long they should be taking them for, they should consult a doctor for advice.

### **Renal Impairment**

Patients with severe renal impairment, with creatinine clearance less than 30 ml/min, the dosage of clarithromycin should be reduced to one half of the normal recommended dose.

Clarithromycin tablets are not recommended for use in children under the age of 12.

This medicine can only be obtained with a prescription.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

### **What benefits of Clarithromycin tablets have been shown in studies?**

Because Clarithromycin tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Klaricid 250 mg and 500 mg Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

### **What are the possible side effects of Clarithromycin tablets?**

Because Clarithromycin tablets are generic medicines and are bioequivalent to the reference medicines, Klaricid 250 mg and 500 mg Tablets, their benefits and possible side effects are taken as being the same as the reference medicines.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Clarithromycin tablets, see section 4 of the package leaflet available on the MHRA website.

### **Why was Clarithromycin tablets approved?**

It was concluded that, in accordance with EU requirements, Clarithromycin tablets has been shown to have comparable quality and to be bioequivalent to Klaricid 250 mg and 500 mg Tablets. Therefore, the MHRA decided that, as for Klaricid 250 mg and 500 mg Tablets; the benefits are greater than the risks and recommended that they can be approved for use.

**What measures are being taken to ensure the safe and effective use of Clarithromycin tablets?**

A risk management plan (RMP) has been developed to ensure that Clarithromycin tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPC) and the package leaflet for Clarithromycin 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.

**Other information about Clarithromycin tablets**

Malta and the UK agreed to grant Marketing Authorisations for Clarithromycin tablets on 09 February 2017. Marketing Authorisations were granted in the UK on 17 February 2017.

The full PAR for Clarithromycin tablets follows this summary.

This summary was last updated in March 2017.

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## I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Clarithromycin 250 mg and 500 mg film-coated tablets (PL 42092/0001-2; UK/H/6183/001-02/DC), are approvable. These products are prescription-only medicines (POM), indicated for the treatment of the following bacterial infections in adults and children 12 years and older, when caused by clarithromycin-susceptible bacteria.

- Bacterial pharyngitis
- Mild to moderate community acquired pneumonia
- Acute bacterial sinusitis (adequately diagnosed)
- Acute exacerbation of chronic bronchitis
- Skin infections and soft tissue infections of mild to moderate severity

Clarithromycin film-coated tablets are also indicated for the eradication of *Helicobacter pylori* in adult patients with *Helicobacter pylori* associated ulcers, in appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing agent.

The applications were submitted using the Decentralised Procedures (DCP), with the UK as Reference Member State (RMS), and Malta as Concerned Member State (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Klaricid 250 mg and 500 mg Tablets, which were originally authorised to Abbott Laboratories (00037/0211 & PL 00037/0254) on 09 April 1991 and 24 March 1994 respectively. These reference licenses underwent change of ownership procedures to BGP Products Ltd (PL 43900/0016-7) on 25 February 2015 and 05 February 2015 and then to the current Marketing Authorisation Holder, Mylan Products Limited (PL 46302/0016-7), on 16 August 2016.

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

With the exception of one bioequivalence study, no new clinical data were provided with these applications. A bioequivalence study was submitted to support these applications, comparing the applicant's test product Clarithromycin 500 mg tablets with the reference product Klaricid 500 mg tablets (Abbott Labs, UK) in healthy, adult, male, human subjects under fasting conditions. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

A summary of the pharmacovigilance system and a detailed risk management plan have been provided with these applications and these are satisfactory.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considered that the applications could be approved at the end of procedure (Day 210) on 09 February 2017. After a subsequent National phase, the UK granted Marketing Authorisations (PL

42092/0001-0002) for these products on 17 February 2017.

## II QUALITY ASPECTS

### II.1 Introduction

The finished product is film-coat tablets containing 250 mg or 500 mg of clarithromycin, as the active ingredient. Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose (PH 101), croscarmellose sodium, colloidal anhydrous silica, powdered cellulose and magnesium stearate making up the film core, and the film coating opadry white OY-L-28900 (lactose monohydrate, hypromellose, titanium dioxide (E171) and macrogol).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of opadry white OY-L-28900 which complies with an inhouse specification and powdered cellulose and magnesium stearate are controlled by the United States Pharmacopeia (USP) monograph. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

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

The finished products are packaged in aluminium/polyvinylchloride (PVC)/blisters containing 14 tablets. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

### II.2 Drug Substance

INN: Clarithromycin

Chemical name: 6-O-Methylerythromycin A

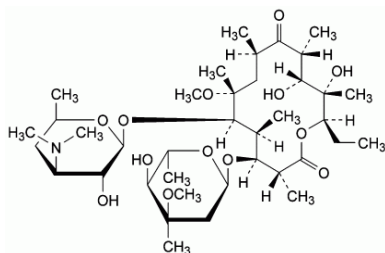
*or*

13-Ethyl-2,4,6,8,10,12-hexamethyl-6-O-methyl-11,12-dihydroxy-9-oxo-3-(3-hydroxy-4-methoxy-2,4-dimethyltetrahydropyran-6-yloxy)-5-(3-hydroxy-4-dimethylamino-6-methyltetrahydro-pyran-2-yloxy)tridecanolide

*or*

(2R,3S,4S,5R,6R,8R,10R,11R,12S,13R)-3-(2,6-Dideoxy-3-C,3-O-dimethyl- $\alpha$ -L-ribo-hexopyranosyloxy)-11,12-dihydroxy-6-methoxy-2,4,6,8,10,12-hexamethyl-9-oxo-5-(3,4,6-trideoxy-3'-dimethylamino- $\beta$ -D-xylohexopyranosyloxy)-pentadecan-13-olide

Structure:



Molecular formula:  $C_{38}H_{69}NO_{13}$

Molecular weight: 747.9 g/mol

Description: white to almost white crystalline powder.

Solubility: Practically insoluble in water, soluble in acetone and in methylene chloride, slightly soluble in methanol.

Clarithromycin is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, clarithromycin, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.



## **II.3. Medicinal Product**

### **Pharmaceutical Development**

The objective of the development programme was to formulate safe, efficacious tablets containing 250 mg or 500 mg of clarithromycin per tablet, that are generic versions of the reference products Klaricid 250 mg and 500 mg Tablets (Mylan Products Limited). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in-vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

### **Manufacture of the products**

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated at pilot scale batch size and have shown satisfactory results. The process validation protocol to be followed for full-scale production batches has been provided and is satisfactory.

### **Finished Product Specifications**

The finished product specifications proposed are acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

### **Stability of the Products**

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months with the storage condition 'Store in the original package'.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

## **II.4 Discussion on chemical, pharmaceutical and biological aspects**

There are no objections to the approval of these applications from a pharmaceutical viewpoint.

## **III NON-CLINICAL ASPECTS**

### **III.1 Introduction**

As the pharmacodynamic, pharmacokinetic and toxicological properties of clarithromycin are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

### **III.2 Pharmacology**

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

### **III.3 Pharmacokinetics**

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

### **III.4 Toxicology**

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

### III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Clarithromycin 250 mg and 500 mg film-coated tablets are intended for generic substitution, their use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

### III.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

## IV CLINICAL ASPECTS

### IV.1 Introduction

The clinical pharmacology of clarithromycin is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of clarithromycin.

Based on the data provided, Clarithromycin 250 mg and 500 mg tablets can be considered bioequivalent to Klaricid 250 mg and 500 mg tablets (Mylan Products Ltd).

### IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence study:

#### STUDY

An open label, balanced, randomised, single-dose, two-treatment two-sequence, two period, crossover bioequivalence study of the applicant's test product Clarithromycin 500 mg tablets versus the reference product Klaricid 500 mg tablets (Mylan Products Ltd) in healthy, adult, male, human subjects under fasting conditions.

Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was 5 days. The pharmacokinetic results are presented below:

**Table 1: Summary of comparative bioequivalence data and 90% Confidence Interval (CI) for clarithromycin:**

PK Parameters	Geometrical Least		Ratio % (T/R)	90% Confidence interval
	Test	Reference		
Ln (C <sub>max</sub> )(ng/ml)	3032.579	2826.165	107.30	96.5 – 119.4
Ln (AUC <sub>0-t</sub> ) (hr*ng/ml)	25913.498	25650.750	101.02	94.8 – 107.6

#### Conclusion

The 90% confidence intervals of the test/reference ratio for AUC<sub>0-t</sub>, and C<sub>max</sub> values for clarithromycin for the 500 mg strength 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 Klaricid 250 mg and 500 mg tablets (Mylan Products Ltd).

As the 250 mg and 500 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 500 mg tablet strength can be extrapolated to the 250 mg strength tablet.

### IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for applications of this type.

### IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for applications of this type.

### IV.5 Clinical safety

No new safety data were submitted and none are required.

### IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The Marketing Authorisation Holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Clarithromycin 250 mg and 500 mg film-coated tablets.

**A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
<b>Important identified risks</b>		
Hypersensitivity	Warning has been provided in SPC Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects and appropriate advice is provided to the prescriber to minimise this risk.	None
Hepatotoxicity	Warning has been provided in SPC Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects and appropriate advice is provided to the prescriber to minimise this risk.	None
Risk of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointes.	Warning has been provided in SPC Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, Section 4.5 Interaction with other medicinal products and other forms of interaction and Section 4.8 Undesirable effects and appropriate advice is provided to the prescriber to minimise this risk.	None
Pseudomembranous colitis	Warning has been provided in SPC Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects and appropriate advice is provided to the prescriber to minimise this risk.	None
Resistance to antibiotics and microorganisms	Warning has been provided in SPC Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects and appropriate advice is provided to the prescriber	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	to minimise this risk.	
Drug-Drug interactions	Warning has been provided in SPC Section 4.5 Interaction with other medicinal products and other forms of interaction and Section 4.8 Undesirable effects and appropriate advice is provided to the prescriber to minimise this risk.	None
Acute renal failure	Warning has been provided in SPC Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use, Section 4.8 Undesirable effects and appropriate advice is provided to the prescriber to minimise this risk.	None
Agranulocytosis	Warning has been provided in SPC Section 4.8 Undesirable effects and appropriate advice is provided to the prescriber to minimise this risk.	None
<b>Important Potential risks</b>		
Psychiatric disorders	Warning has been provided in SPC Section 4.8 Undesirable effects and appropriate advice is provided to the prescriber to minimise this risk.	None
<b>Missing Information</b>		
Use in pregnancy and lactation	Warning has been provided in Section 4.4 Special warnings and precautions for use and Section 4.6 Pregnancy and lactation and appropriate advice is provided to the prescriber to minimise this risk.	None
Use in children below 12 years of age	Warning has been provided in SPC Section 4.2 Posology and method of administration and Section 4.8 Undesirable effects and appropriate advice is provided to the prescriber to minimise this risk.	None

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

#### IV.7 Discussion on the clinical aspects

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant's test product Clarithromycin 250 mg and 500 mg tablets and the reference product Klaricid 250 mg and 500 mg tablets (Mylan Products Ltd).

The grant of Marketing Authorisations is recommended for these applications.

#### V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use*.

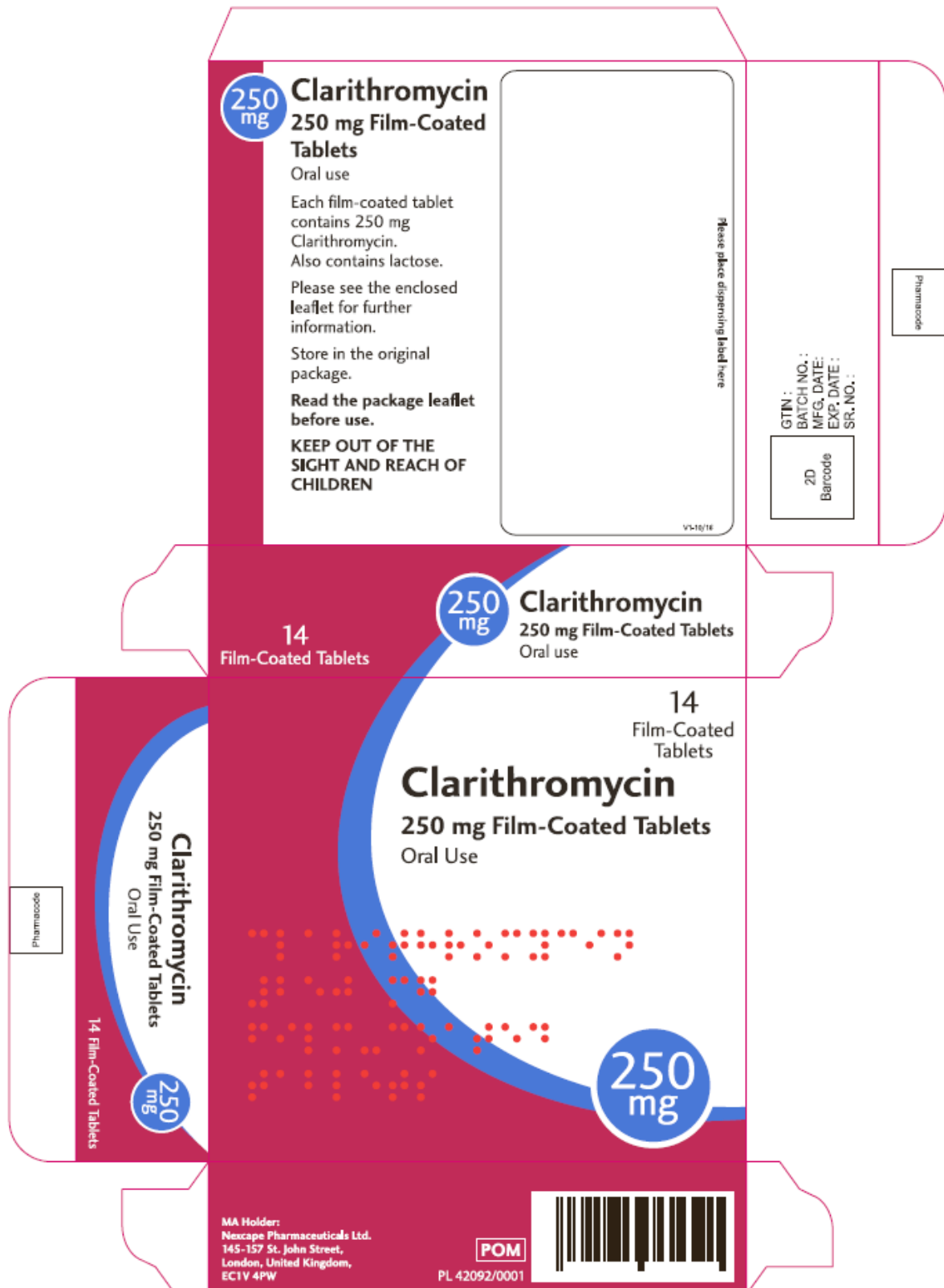
**VI Overall conclusion, benefit/risk assessment and recommendation**

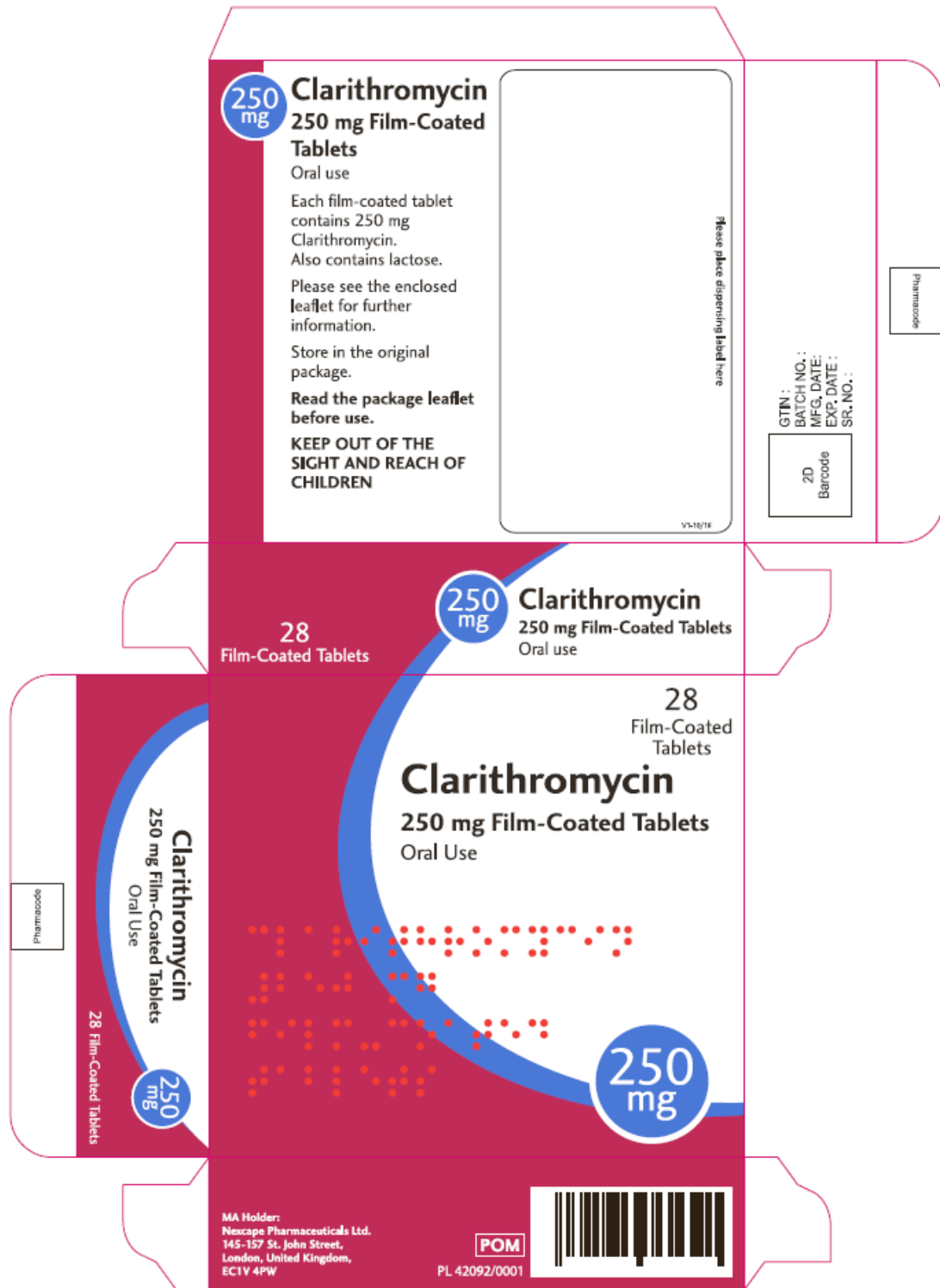
The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with clarithromycin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

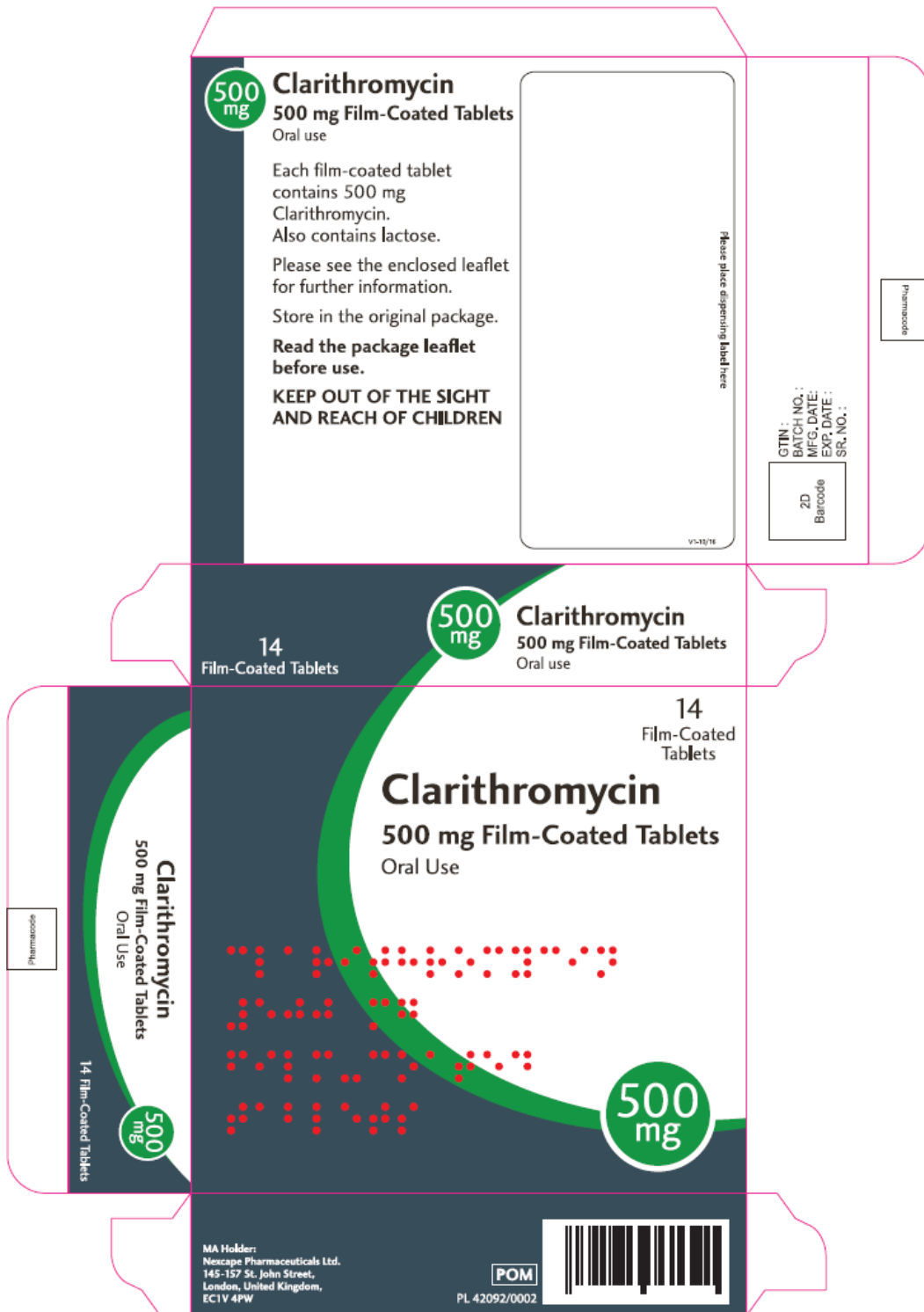
The approved labelling for Clarithromycin 250 mg and 500 mg film-coated tablets is presented below:

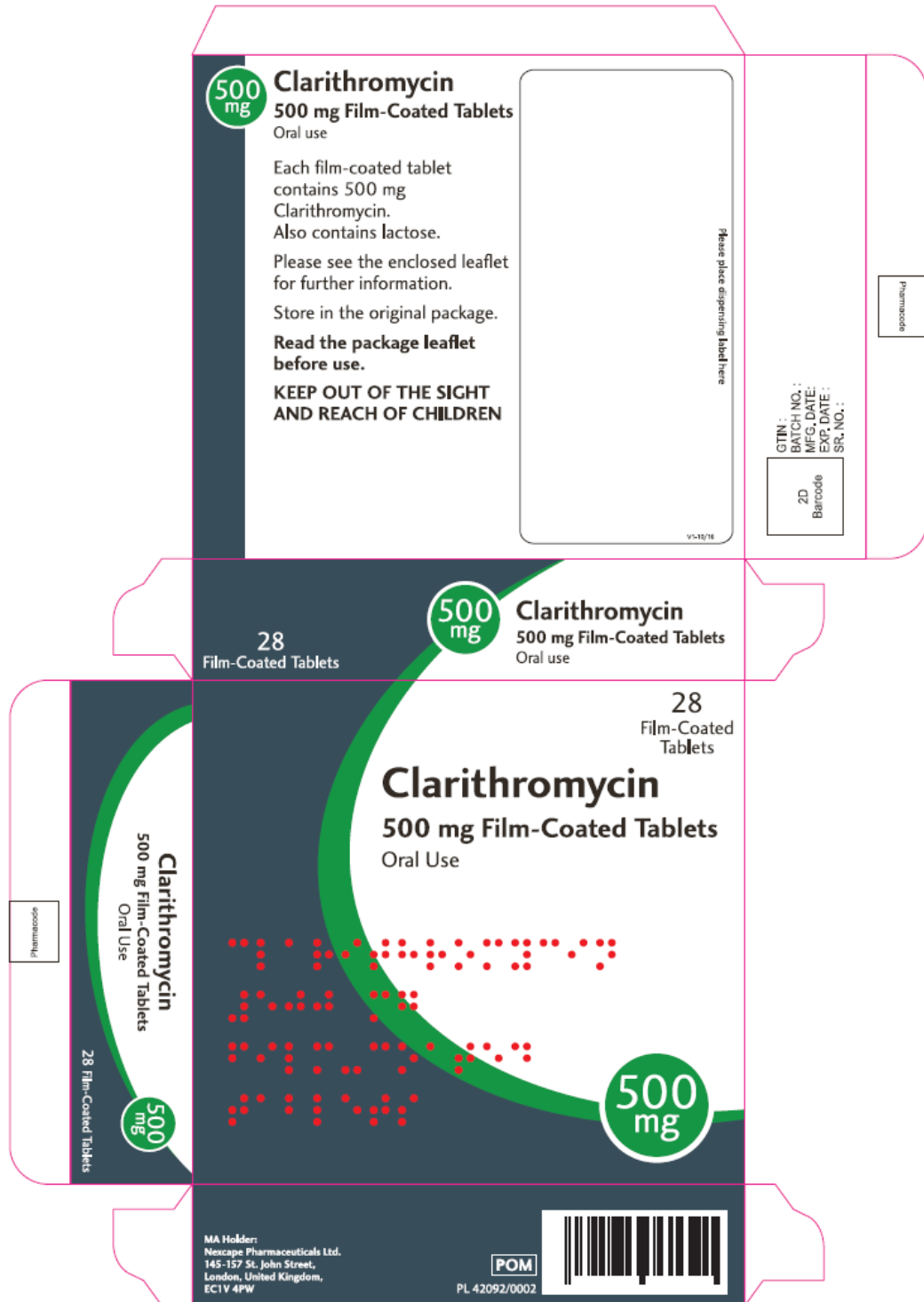




EMBOSSING ZONE	<b>Clarithromycin 250mg Film-Coated Tablets</b> Clarithromycin MA Holder: Nexscape Pharmaceuticals Ltd.	<b>Clarithromycin 250mg Film-Coated Tablets</b> Clarithromycin MA Holder: Nexscape Pharmaceuticals Ltd.	<b>Clarithromycin 250mg Film-Coated Tablets</b> Clarithromycin MA Holder: Nexscape Pharmaceuticals Ltd.
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EMBOSSING ZONE	<b>Clarithromycin 500mg Film-Coated Tablets</b> Clarithromycin MA Holder: Nexcape Pharmaceuticals Ltd.	<b>Clarithromycin 500mg Film-Coated Tablets</b> Clarithromycin MA Holder: Nexcape Pharmaceuticals Ltd.	<b>Clarithromycin 500mg Film-Coated Tablets</b> Clarithromycin MA Holder: Nexcape Pharmaceuticals Ltd.
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## Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<b>Scope</b>	<b>Procedure number</b>	<b>Product information affected</b>	<b>Date of start of the procedure</b>	<b>Date of end of procedure</b>	<b>Approval/non approval</b>	<b>Assessment report attached Y/N (version)</b>