Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Co-amoxiclav 250 mg/125 mg film-coated tablets

(Amoxicillin and clavulanic acid)

UK Licence No: PL 16363/0540

Milpharm Limited

LAY SUMMARY
Co-amoxiclav 250 mg/125 mg film-coated tablets
(Amoxicillin and clavulanic acid)

This is a summary of the Public Assessment Report (PAR) for Co-amoxiclav 250 mg/125 mg film-coated tablets (PL 16363/0540). It explains how Co-amoxiclav 250 mg/125 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 Co-amoxiclav 250 mg/125 mg film-coated tablets.

For ease of reading, this medicinal product will be referred to as Co-amoxiclav tablets in this Lay Summary.

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

What are Co-amoxiclav tablets and what are they used for?
Co-amoxiclav tablets are a generic medicine. This means that Co-amoxiclav tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Augmentin 375 mg film-coated tablets (PL 00038/0270; Beecham Group Plc, UK).

Co-amoxiclav tablets are used in adults and children to treat the following infections:
- sinus infections
- urinary tract infections
- Skin infections
- dental infections

How do Co-amoxiclav tablets work?
This medicine contains the active ingredients, amoxicillin and clavulanic acid. Amoxicillin is an antibiotic that belongs to a group of medicines called penicillins. Amoxicillin works by killing the bacteria that cause the infection. Amoxicillin can sometimes be stopped from working (made inactive). The other active component, clavulanic acid, stops this from happening.

How are Co-amoxiclav tablets used?
Co-amoxiclav tablets are taken by mouth. The tablets should be swallowed whole with water at the start of a meal or slightly before. The doses must be spaced out evenly during the day, at least four hours apart. Patients should not take two doses in 1 hour and must not take this medicine for more than two weeks. If patients still feel unwell they should go back and see a doctor.

Patients must take this medicine exactly as a doctor or pharmacist has told them.

The usual dose in adults and children weighing 40 kg and over is one tablet three times a day.

Children weighing less than 40 kg
Co-amoxiclav tablets are not recommended in children aged 6 years or less. They should preferably be treated with Co-amoxiclav oral suspension or sachets.
The dose in patients with kidney and liver problems might be changed. A different strength or different medicine may be chosen by a doctor.

Patients with liver problems may have more frequent blood tests to check the liver is working.

This medicine can only be obtained on prescription from a doctor.

For further information on how Co-amoxiclav tablets are used, please refer to the Summary of Product Characteristics and the Patient Information Leaflet (PIL) available on the MHRA website.

How have Co-amoxiclav tablets been studied?
Because Co-amoxiclav tablets are a generic medicine, studies have been limited to tests to determine that it is bioequivalent to the reference medicine, Augmentin 375 mg film-coated tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Co-amoxiclav tablets?
Because Co-amoxiclav tablets are a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

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

Why are Co-amoxiclav tablets approved?
It was concluded that, in accordance with EU requirements, Co-amoxiclav tablets have been shown to have comparable quality and to be bioequivalent to Augmentin 375 mg film-coated tablets. Therefore, the MHRA concluded that, as for Augmentin 375 mg film-coated tablets, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Co-amoxiclav tablets?
A Risk Management Plan (RMP) has been developed to ensure that Co-amoxiclav 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 Co-amoxiclav 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 Co-amoxiclav tablets
A Marketing Authorisation was granted in the UK on 06 September 2018.

The full PAR for Co-amoxiclav tablets follows this summary.

This summary was last updated in November 2018.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Milpharm Limited a Marketing Authorisation for the medicinal product Co-amoxiclav 250 mg/125 mg film-coated tablets (PL 16363/0540) on 06 September 2018. This prescription only medicine (POM), is indicated for the treatment of the following infections in adults and children:

- Acute bacterial sinusitis (adequately diagnosed)
- Cystitis
- Pyelonephritis
- Cellulitis
- Animal bites
- Severe dental abscess with spreading cellulitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The application was submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant has cross referred to Augmentin 375 mg film-coated tablets, first authorised to Beecham Group Plc (PL 00038/0270) on 03 April 1981.

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

No new non-clinical studies were conducted, which is acceptable given that this is a generic application of an originator product that has been in clinical use for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacturing and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

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

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 Co-amoxiclav 250 mg/125 mg film-coated tablets outweigh the risks and Marketing Authorisations were granted.

II QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains amoxicillin trihydrate equivalent to 250 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid as active ingredients. The excipients present are cellulose, microcrystalline, crospovidone (Type B), sodium starch glycolate (Type A), ethyl cellulose dispersion (Type B), silica, colloidal anhydrous and magnesium stearate making up the tablet core. The tablet coat is composed of hypromellose 2910 (5cps), hypromellose 2910 (15cps), macrogol 4000, macrogol 6000 and titanium dioxide (E171).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of ethyl cellulose dispersion (Type B) which complies with a national formulary (NF). Satisfactory Certificates of Analysis have been provided for these excipients.

None of the excipients is of animal or human origin. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

The finished product is packaged in alu-alu (polyamide/aluminium/polyvinylchloride (PVC) - aluminium foil) blister pack, containing 21 tablets.

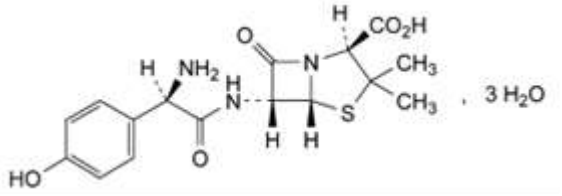
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substances

INN: Amoxicillin trihydrate

Chemical names: (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate

Structural formula:



Molecular formula: $C_{16}H_{19}N_3O_5S.3H_2O$

Molecular mass: 419.4 g/mol

Appearance: White or almost white, crystalline powder.

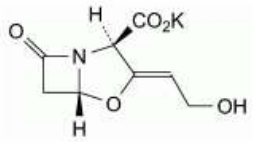
Solubility: Amoxicillin trihydrate is slightly soluble in water, very slightly soluble in ethanol (96 per cent) and practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

Amoxicillin trihydrate is the subject of a European Pharmacopoeia monograph.

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

INN: Potassium clavulanate

Chemical names: potassium (2*R*,3*Z*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate
Structural formula:



Molecular formula: $C_8H_8KNO_5$
Molecular mass: 237.3 g/mol
Appearance: White or almost white powder, hygroscopic (diluted).
Solubility: Potassium clavulanate is freely soluble in water, slightly soluble in ethanol (96 per cent) and very slightly soluble in acetone (diluted).

Potassium clavulanate is the subject of a European Pharmacopoeia monograph.

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

II.3 Medicinal Product

Pharmaceutical Development

The aim of the development programme was to formulate safe, efficacious and stable tablets containing 250 mg amoxicillin and 125 mg clavulanic acid as active ingredients.

Suitable pharmaceutical development data have been provided for this application.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years with a storage condition “Store in the original blister in order to protect from light and moisture” has been set. This is satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of amoxicillin and clavulanic acid 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 Co-amoxiclav 250 mg/125 mg film-coated tablets contains only active substances of well-established use, it will not lead to an increase of the environmental exposure to these substances. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of amoxicillin and clavulanic acid 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 this application.

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 amoxicillin and clavulanic acid.

Based on the data provided, Amoxicillin/Clavulanic acid 250/125 mg film-coated tablets can be considered bioequivalent to Augmentin 250/125 mg tablets (GlaxoSmithKline, UK).

IV.2 Pharmacokinetics

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

An open label, randomised, two treatment, two sequence, four period, replicate, cross-over, single-dose comparative oral bioavailability study of Amoxicillin/Clavulanic acid 250/125 mg film-coated tablets of the applicant's test product versus the reference product, Augmentin 250/125 mg tablets (GlaxoSmithKline, UK) in healthy, adult, male subjects under fed conditions.

A single oral dose of 250/125mg tablets of test (T) or reference (R) product was administered along with 240 ml of water 30 minutes after a high calorie, high fat breakfast following an overnight fast of at least 10 hours pre-dose. A standard meal was served 5 hours post dose. Drinking water was not allowed for 1

hour before and 2 hours after dosing. A washout period of 7 days was observed between the treatment schedules.

Two pre-dose (0.00 hour) blood samples of 4 mL each were collected in period I and a single pre-dose (0.00 hour) blood sample of 4 mL was collected in period II, III and IV before the drug administration. The post-dose blood samples were collected up to and including 12.00 hours.

The pharmacokinetic results are presented below:

Table 1: Pharmacokinetic parameters (ratios, power and 90% confidence Interval from LSM) Amoxicillin

Parameters	Ln-transformed Data		
	(T/R) % Ratio	90% Confidence Interval	Power (%)
C_{max}	98.99	94.28-103.92	100
AUC_{0-t}	98.02	96.36-99.71	100
$AUC_{0-\infty}$	98.10	96.49-99.73	100

Table 2: Pharmacokinetic parameters (ratios, power and 90% confidence Interval from LSM) Clavulanic acid

Parameters	Ln-transformed Data		
	(T/R) % Ratio	90% Confidence Interval	Power (%)
C_{max}	96.51	85.81-108.54	93
AUC_{0-t}	94.01	85.38-103.52	98
$AUC_{0-\infty}$	93.96	85.40-103.38	99

Study conclusion
The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for amoxicillin and clavulanic acid 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 Co-amoxiclav 250 mg/125 mg film-coated tablets is bioequivalent to the reference product, Augmentin 250/125 mg tablets (GlaxoSmithKline, UK).

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)
The Marketing Authorisation Holder has submitted a risk management plan, 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 Co-amoxiclav 250 mg/125 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
Important Identified Risks		
Hypersensitivity reactions (anaphylactoid)	Text in SmPC section 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Convulsions	Text in SmPC Section 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 4.9 Overdose	None
Prolonged use result in overgrowth of non- susceptible organisms	Text in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects	None
Acute generalised exanthemous pustulosis (AGEP)	Text in SmPC section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects	None
Hepatic events	Text in SmPC Section 4.2 Posology and method of administration, 4.3 contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects	None
Antibiotic-associated colitis	Text in SmPC Section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None
Concomitant use with oral anticoagulants	Text in SPC Section 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction and 4.8 Undesirable effects	None
Morbilliform rash	Text in SmPC Section 4.4 Special warnings and precautions for use	None
Concomitant use with allopurinol	Text in SmPC Section 4.4 Special warnings and precautions for use	None
Use in patients with renal impairment	Text in SmPC Section 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use	None
Crystalluria	Text in SmPC Section 4.4 Special warnings and precautions for use, 4.8	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Undesirable effects and 4.9 Overdose.	
Effects on Laboratory test results	Text in SmPC Section 4.4 Special warnings and precautions for use	None
Important Potential Risks		
None		
Missing information		
Use in Pregnancy or Lactation	Text in SmPC section 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data	None

Routine risk minimisation is provided through the summary of product characterisation and the patient information leaflet. No additional risk minimisation measures are planned for this product.

Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended for this application.

V USER CONSULTATION

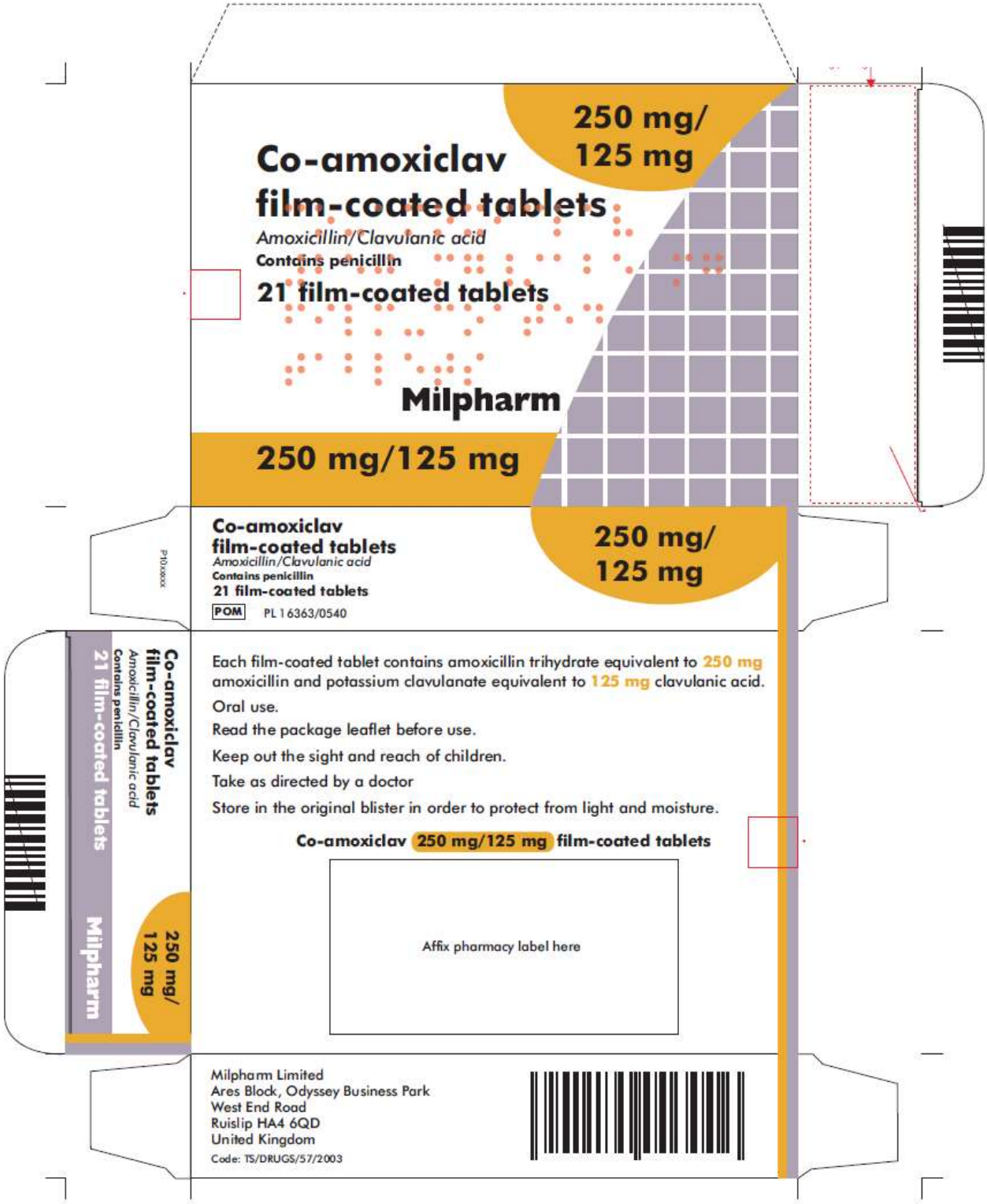
User testing of the package leaflet has been accepted, based on bridging reports provided by the applicant making reference to the user-testing of the PIL for the reference product Augmentin 375mg tablets which is also in line with the PIL of Co-amoxiclav 500/125 mg tablets (parent PIL) (Aurobindo Pharma Limited UK; NL/H/1707/01/MR). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with amoxicillin and clavulanic acid is considered to have demonstrated the therapeutic value of the compounds. 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 Co-amoxiclav 250 mg/125 mg film-coated tablets is presented below:




Co-Amoxiclav 250 mg/125 mg film coated tablets
amoxicillin/ davulanic acid
Milpharm Limited
Lot / EXP:
Code: TS/DMUGS/57/2003

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, commitment

Date submitted	Application type	Scope	Outcome