

**Co-Amoxiclav 250 mg/ 62.5 mg/ 5 ml Powder for Oral
Suspension**

Amoxicillin trihydrate and clavulanic potassium salt

PL 21880/0010

UKPAR

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Co-Amoxiclav 250 mg/62.5 mg/5 ml Powder for Oral Suspension**Amoxicillin trihydrate and clavulanic potassium salt****PL 21880/0010****LAY SUMMARY**

On 20th December 2012, the MHRA granted Medreich PLC a Marketing Authorisation (licence) for the medicinal product Co-Amoxiclav 250 mg/ 62.5 mg/ 5 ml Powder for Oral Suspension (PL 21880/0010). This medicine is only available on prescription from your doctor.

Co-Amoxiclav is an antibiotic and works by killing bacteria that cause infections. It contains two different medicines called amoxicillin and clavulanic acid. Amoxicillin belongs to a group of medicines called “penicillins” that can sometimes be stopped from working (made inactive). The other active component (clavulanic acid) stops this from happening.

Co-Amoxiclav is used in babies and children to treat the following infections:

- middle ear and sinus infections
- respiratory tract infections
- urinary tract infections
- skin and soft tissue infections including dental infections
- bone and joint infections.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Co-Amoxiclav 250 mg/ 62.5 mg/ 5 ml Powder for Oral Suspension outweigh the risks. Hence, a Marketing Authorisation has been granted.

Co-Amoxiclav 250 mg/ 62.5 mg/ 5 ml Powder for Oral Suspension

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a Marketing Authorisation for the medicinal product Co-Amoxiclav 250 mg/ 62.5 mg/ 5 ml Powder for Oral Suspension (PL 21880/0010) on 20th December 2012. This is a prescription only medicine (POM) used in treatment of the following infections in adults and children:

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

This is a national abridged application for Co-Amoxiclav 250 mg/ 62.5 mg/ 5 ml Powder for Oral Suspension submitted under Article 10(1) of Directive 2001/83/EC, as amended. This product is cross-referring to Augmentin 250/ 62.5 mg SF Suspension (PL 00038/0337), authorised to Beechams Group PLC on 20th March 1987.

Amoxicillin is a semi-synthetic 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.

A pharmacovigilance system has been provided with this application and is satisfactory.

PHARMACEUTICAL ASSESSMENT

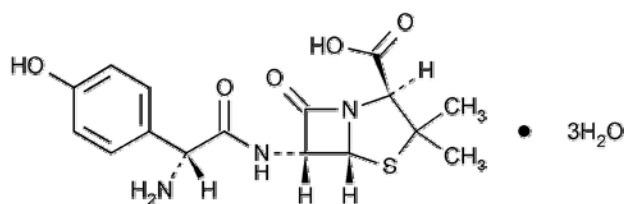
DRUG SUBSTANCE

Nomenclature

rINN: Amoxicillin trihydrate

Chemical Names: (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate [CAS number: 61336-70-7].

Structure:



Molecular Formula: C₁₆H₁₉N₃O₅S·3H₂O

Molecular Weight: 419.4 g/mol

Appearance: A white or almost white, crystalline powder, slightly soluble in water, very slightly soluble in ethanol and practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

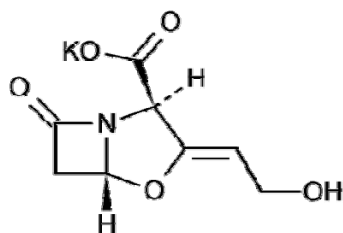
Amoxicillin trihydrate is the subject of a European Pharmacopoeia monograph.

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

rINN: Potassium clavulanate

Chemical Names: (*Z*)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate [CAS number: 61177-45-5].

Structure:



Molecular Formula: $C_8H_8KNO_5$

Molecular Weight: 237.3 g/mol

Appearance: A white or almost white, crystalline powder, freely soluble in water, slightly soluble in alcohol and very slightly soluble in acetone.

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 a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients xanthan gum (E415), aspartame (E951), silicon dioxide (E551), colloidal silica, anhydrous citric acid, hypromellose, flavour orange dry powder, flavour raspberry dry powder and flavour golden dry powder

All excipients used comply with their respective British Pharmacopoeia monographs with the exception of flavour orange dry powder, flavour raspberry dry powder and flavour golden dry powder which are covered by an in-house specification. The excipient silicon dioxide (E551) complies with the United States national formulary. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has confirmed that none of the excipients are of animal or human origin.

Pharmaceutical development

Suitable pharmaceutical development data have been provided for this application. Comparable impurity profiles are provided for this product versus the originator product.

Manufacture

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 at pilot-scale and has shown satisfactory results. A process validation study on the full- scale commercial batches has been conducted.

Finished product specification

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

Container Closure System

The product is supplied in glass round shaped bottles containing an off-white dry powder. Each bottle is fitted with polypropylene child resistant cap and packed in a carton with a 20 ml measuring cup with 2.5 ml graduations.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability

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

Based on the results, shelf-lives of 24 months for dry powder and 7 days for reconstituted suspension when stored in refrigerator (2-8°C) have been set.

The storage conditions for the powder for suspension are “Do not store above 25°C” and “Keep the bottle tightly closed” and for the reconstituted suspension “Store in a refrigerator at 2-8°C” and “Do not freeze”. These are satisfactory.

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

The SmPC, PIL and labelling are pharmaceutically satisfactory.

User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the user-testing of the PIL for Co-Amoxiclav 457 mg / 5 ml Suspension (PL 21880/0011). 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 of the rationale for bridging is accepted

Marketing Authorisation Application (MAA) Form

The MAA form is pharmaceutically satisfactory.

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

There are no objections to the approval of this product from a pharmaceutical point of view.

NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of amoxicillin trihydrate and potassium clavulanate are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

Suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

BIOEQUIVALENCE

In support of this application, the Marketing Authorisation holder has submitted the following bioequivalence study:

This is an open label, randomised, 2 period, 2 treatment, 2 sequence, two way cross-over, single dose bioequivalence study comparing the test product, Fleming 312.5 mg/5 ml oral suspension with the reference product Augmentin 250 mg/5 ml oral suspension in healthy male volunteers under fasting conditions.

Blood samples were collected pre-dose and at 0.33, 0.66, 1.0, 1.33, 1.66, 2.0, 2.33, 2.66, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0 and 12.0 hours post dose. A washout period of 7 days was maintained between the two periods.

Amoxicillin and internal standard Hydroxyzine were determined with HPLC-MS/MS after sample preparation was performed with Solid Phase extraction.

Clavulanic acid and internal standard salicylic acid were determined with HPLC UV detector after sample preparation with protein precipitation using dichloromethane.

Results

Relative bioavailability assessments for Amoxicillin after oral administration of Fleming Oral Suspension (Test Formulation) and Augmentin[®] 250/62 SF suspension (Reference Formulation) (n=30):

Pharmacokinetic Parameters	90% Confidence Intervals, Ratio and Intra-subject Variability (n=30)		
	90% C.I.	Ratio of Geometric Means (%)	Intra-Subject %CV
AUC _(0-t)	89.59% to 100.87%	95.06%	13.53%
AUC _(0-∞)	89.78% to 100.94%	95.20%	13.36%
C _{max}	85.68% to 95.72%	90.56%	12.64%

Relative bioavailability assessments for Clavulanic Acid after oral administration of Fleming Oral Suspension (Test Formulation) and Augmentin[®] 250/62 SF suspension (Reference Formulation)(n=30):

Pharmacokinetic Parameters	90% Confidence Intervals, Ratio and Intra-subject Variability (n=30)		
	90% C.I.	Ratio of Geometric Means (%)	Intra-Subject %CV
AUC _(0-t)	102.27% to 119.54%	110.57%	17.86%
AUC _{(0-∞)*}	100.70% to 118.97%	109.45%	17.31%
C _{max}	98.60% to 112.64%	105.38%	15.21%

*No. of subjects taken into calculation = 25

The 90% confidence intervals for C_{max} and AUC were within the pre-defined limits. Bioequivalence has been shown for the test formulation (Fleming 312.5 mg/5 ml oral suspension) and the reference formulation (Augmentin 250 mg/5 ml oral suspension).

EFFICACY

No new efficacy data have been submitted and none are required for this application.

SAFETY

No new safety data have been submitted and none are required for this application.

EXPERT REPORT

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS

This is satisfactory.

PATIENT INFORMATION LEAFLET

This is satisfactory.

LABELLING

This is satisfactory

MAA FORMS

This is satisfactory.

CONCLUSIONS

There are no objections to the approval of this product from a clinical point of view.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Co-Amoxiclav 250 mg/ 62.5 mg/ 5 ml Powder for Oral Suspension 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 and none are required for applications of this type.

EFFICACY

No new data have been submitted and none are required for applications of this type.

Bioequivalence have been demonstrated between the applicant's Fleming 312.5 mg/5 ml oral suspension and the reference product, Augmentin 250 mg/5 ml oral suspension.

SAFETY

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The SmPC and PIL are satisfactory and consistent with those for the reference product. Satisfactory labelling has also been submitted.

RISK BENEFIT 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 amoxicillin trihydrate and potassium clavulanate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Co-Amoxiclav 250 mg/62.5 mg/5 ml Powder for Oral Suspension**Amoxicillin trihydrate and clavulanic potassium salt****PL 21880/0010****STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the Marketing Authorisation application on 3 rd January 2006
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 8 th February 2006
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 17 th May 2006, 17 th March 2008, 31 st October 2008 and on the clinical section 30 th June 2006 and 2 nd December 2012
4	The applicant responded to the MHRA's requests, providing further information to the quality section on 1 st February 2008, 22 nd September 2008, 30 th December 2008 and on the clinical section on 3 rd March 2008 and 14 th June 2012
5	The application was determined on 20 th December 2012.

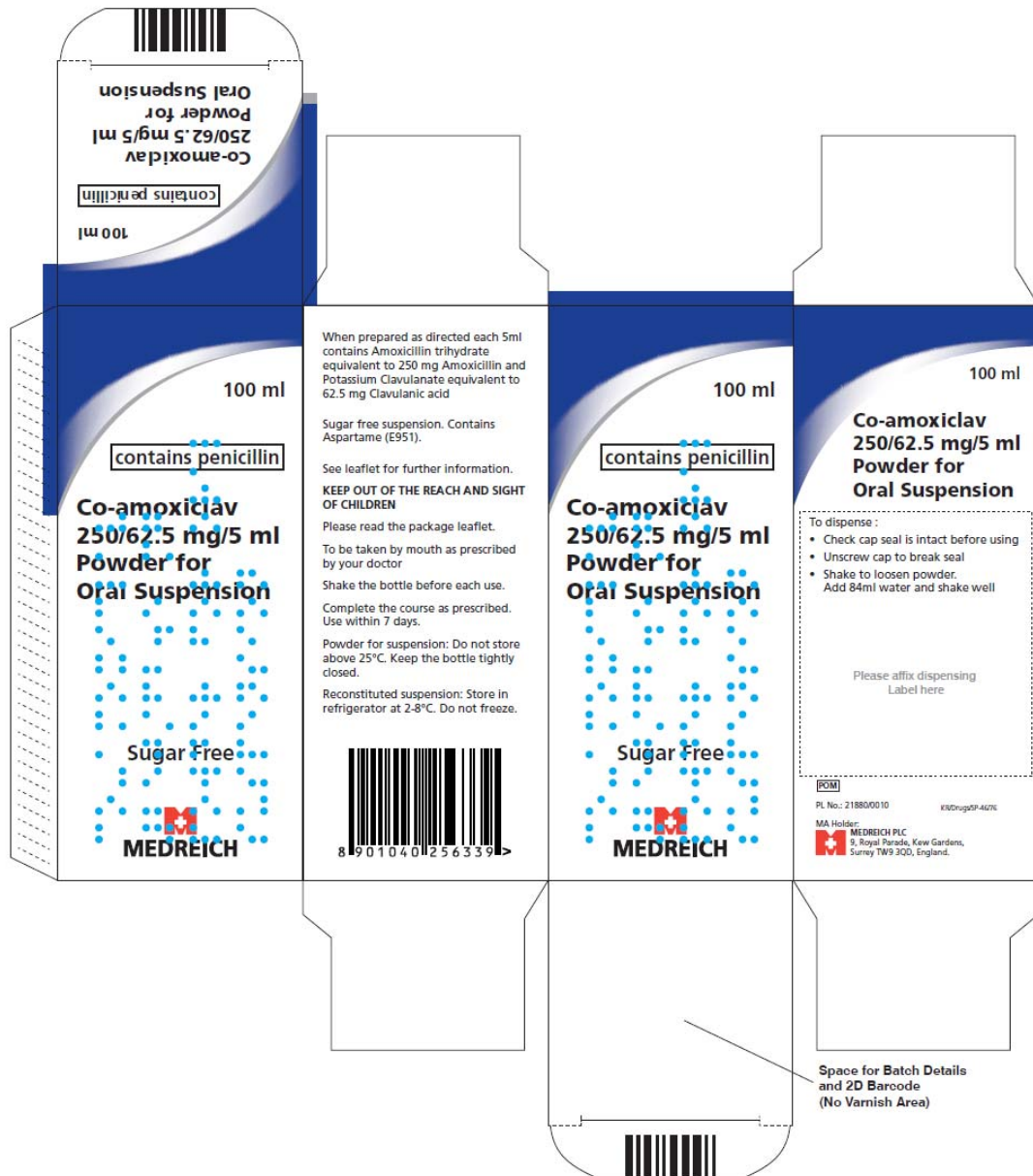
SUMMARY OF PRODUCT CHARACTERISTICS

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

LABELLING



When prepared as directed each 5 ml contains Amoxicillin trihydrate equivalent to 250 mg Amoxicillin and Potassium Clavulanate equivalent to 62.5 mg Clavulanic acid. Sugar free suspension. Contains Aspartame (E951). See leaflet for further information.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Please read the package leaflet. To be taken by mouth as prescribed by your doctor.

Shake the bottle before each use.

Complete the course as prescribed.

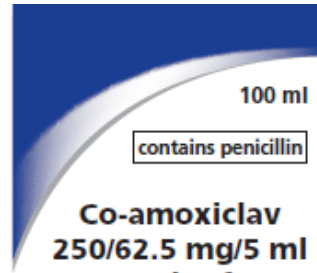
Use within 7 days.

Powder for suspension:

Do not store above 25°C. Keep the bottle tightly closed.

Reconstituted suspension: Store in refrigerator at 2-8°C. Do not freeze.

KR/Drugs/SP-46/76



**Co-amoxiclav
250/62.5 mg/5 ml
Powder for
Oral Suspension**

Sugar Free


MEDREICH


To dispense :

- Check cap seal is intact before using
- Unscrew cap to break seal
- Shake to loosen powder. Add 84ml water and shake well

POM

PL No.: 21880/0010

MA Holder:

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