Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Amoxicillin 500 mg/ 5 ml Powder for oral suspension

(amoxicillin trihydrate)

PL 48468/0017

Vivalabs Europe Limited

LAY SUMMARY

Amoxicillin 500 mg/ 5 ml Powder for oral suspension

(amoxicillin trihydrate)

This is a summary of the Public Assessment Report (PAR) for Amoxicillin 500 mg/ 5 ml Powder for oral suspension. It explains how this product 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 this product.

This product will be referred to as Amoxicillin Powder for oral suspension in this lay summary for ease of reading.

For practical information about using Amoxicillin Powder for oral suspension, patients should read the package leaflet or contact their doctor or pharmacist.

What is Amoxicillin Powder for oral suspension and what is it used for?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the European Union (EU) called Clamoxyl 500 mg/5 ml, poudre pour suspension buvable.

Amoxicillin Powder for oral solution is used to treat infections caused by bacteria in different parts of the body. Amoxicillin Powder for oral suspension may also be used in combination with other medicines to treat stomach ulcers.

How does Amoxicillin Powder for oral suspension work?
This medicine contains the active substance amoxicillin (as amoxicillin trihydrate), which is an antibiotic. Amoxicillin belongs to a group of medicines called “penicillins”.

How is Amoxicillin Powder for oral suspension used?
The pharmaceutical form of this medicine is powder for oral suspension and the route of administration is oral (by mouth).

The patient or caregiver should shake bottle well before each dose. The doses should be spaced evenly during the day, at least 4 hours apart.

The usual dose is:

Children weighing less than 40 kg
All doses are worked out depending on the child's body weight in kilograms.
- The patient’s doctor will advise on how much amoxicillin the caregiver should give to their baby or child.
- The usual dose is 40 mg to 90 mg for each kilogram of body weight a day, given in two or three divided doses.
- The maximum recommended dose is 100 mg for each kilogram of body weight a day.

Adults, elderly patients and children weighing 40 kg or more
This medicine is not usually prescribed for adults and children weighing 40 kg or more. The patient or caregiver should ask their doctor or pharmacist for advice.

Kidney problems
If the patient has kidney problems the dose might be lower than the usual dose.

For further information on how Amoxicillin Powder for oral suspension isused, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

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

What benefits of Amoxicillin Powder for oral suspension have been shown in studies?
Because Amoxicillin Powder for oral suspension is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Amoxicillin Powder for oral suspension ?
Because Amoxicillin Powder for oral suspension is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why was Amoxicillin Powder for oral suspension approved?
It was concluded that, in accordance with EU requirements, Amoxicillin Powder for oral suspension has been shown to be comparable to and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Amoxicillin Powder for oral suspension
A Risk Management Plan (RMP) has been developed to ensure that Amoxicillin Powder for oral suspension is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, 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 and reviewed continuously.

Other information about Amoxicillin Powder for oral suspension
A Marketing Authorisation for Amoxicillin Powder for oral suspension was granted in the UK on 09 January 2020.

The full PAR for Amoxicillin Powder for oral suspension follows this summary.

This summary was last updated in March 2020.

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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) considered that the application for Amoxicillin 500 mg/ 5 ml Powder for oral suspension (PL 48468/0017) could be approved.

Amoxicillin 500 mg/ 5 ml Powder for oral suspension is approved for the treatment of the following infections in adults and children:

- acute bacterial sinusitis
- acute otitis media
- acute streptococcal tonsillitis and pharyngitis
- acute exacerbations of chronic bronchitis
- community acquired pneumonia
- acute cystitis
- asymptomatic bacteriuria in pregnancy
- acute pyelonephritis
- typhoid and paratyphoid fever
- dental abscess with spreading cellulitis
- prosthetic joint infections
- *Helicobacter pylori* eradication
- Lyme disease

Amoxicillin 500 mg/ 5 ml Powder for oral suspension is also indicated for the prophylaxis of endocarditis.

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

Amoxicillin is a semi-synthetic aminopenicillin almost completely absorbed from the gastrointestinal tract in contrast to ampicillin, which is only partially absorbed. The bactericidal effect of amoxicillin results from inhibition of bacterial cell wall synthesis. It is not active against beta-lactamase producing organisms.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic medicine of a suitable originator medicinal product, Clamoxyl 500 mg/5 ml, poudre pour suspension buvable that has been licensed within the EU for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation was granted for this product on 09 January 2020.

II QUALITY ASPECTS

II.1 Introduction

This product consists of 500 mg of amoxicillin ,in the form of amoxicillin trihydrate, in each 5 ml dose of reconstituted oral suspension.

In addition to amoxicillin trihydrate, this product also contains the excipients silicon dioxide, aspartame (E 951), xanthan gum, sodium benzoate (E211), trisodium citrate dihydrate, colloidal silicon dioxide, strawberry flavour and benzyl alcohol.

The finished product is packaged in either 150 ml high density polyethylene (HDPE) bottles, each containing 100 ml of product or 115 ml HDPE bottles, each containing 60 ml of product, closed with polypropylene child resistant caps containing polymers liners. These primary packs are placed in a carton with or without a dosing syringe of 5 ml.

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.

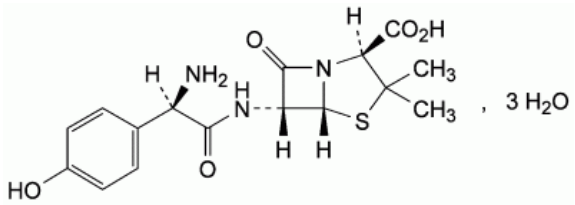
II.2 ACTIVE SUBSTANCE

rINN: **Amoxicillin trihydrate**

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

Molecular Formula: $C_{16}H_{19}N_3O_5S * 3H_2O$

Chemical Structure:



Molecular Weight: 419.1 g/mol

Appearance: White or almost white, crystalline powder

Solubility: Amoxicillin trihydrate is slightly soluble in water, very slightly soluble in ethanol (96 %), 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 are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative dissolution profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final products

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

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

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.

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

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, the following shelf life and storage conditions are accepted:

- dry powder: a shelf life of 2 years, with the storage conditions 'Do not store above 25°C'
- reconstituted suspension: a shelf life of 14 days, with the storage conditions 'Store up to 14 days at 2°C – 8°C in a refrigerator.'

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
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of amoxicillin trihydrate is well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of amoxicillin trihydrate are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following study.

This study was an open label, randomised, two-treatment, two-sequence, two-period, crossover, single dose, oral bioequivalence study comparing the test product Amoxicillin for oral suspension 500 mg/5 ml versus the reference product Amoxil (Amoxicillin) 500 mg/5 ml Powder for oral suspension in subjects under fasted conditions.

Subjects were administered a single dose (5 ml of suspension containing amoxicillin 500 mg) of reconstituted suspension of either the test or reference product using a graduated syringe with 240±2 ml of water, following an overnight fast of at least 10 hours.

Blood samples were taken pre-dose and up to 12 hours post dose, with a washout period of four days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Table 1 Bioequivalence criteria as reported in the bioequivalence study for amoxicillin

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference (%)	90% Confidence Intervals	Intra-Subject CV%[1]
$AUC_{(0-t)}$	93.8	91.01 - 96.62	7.8
C_{max}	94.6	90.66 - 98.66	11.1

C_{max} maximum plasma concentration
AUC_{0-t} area under the plasma concentration-time curve from zero to t hours
CV coefficient of variability
[1]Estimated from the Residual Means Squares

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

The Patient Information Leaflet (PIL) 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 results show that the PIL 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.

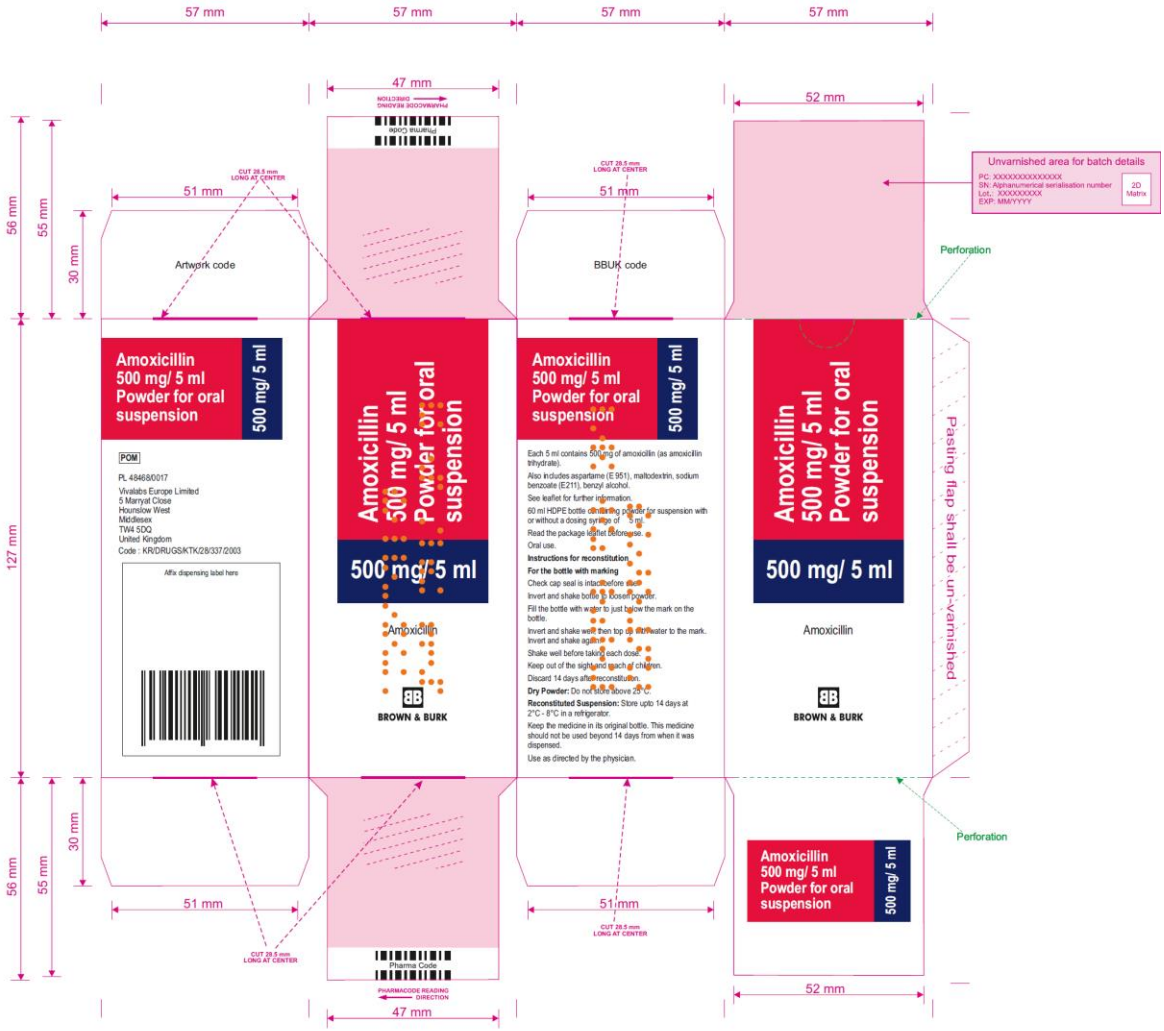
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product is available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.



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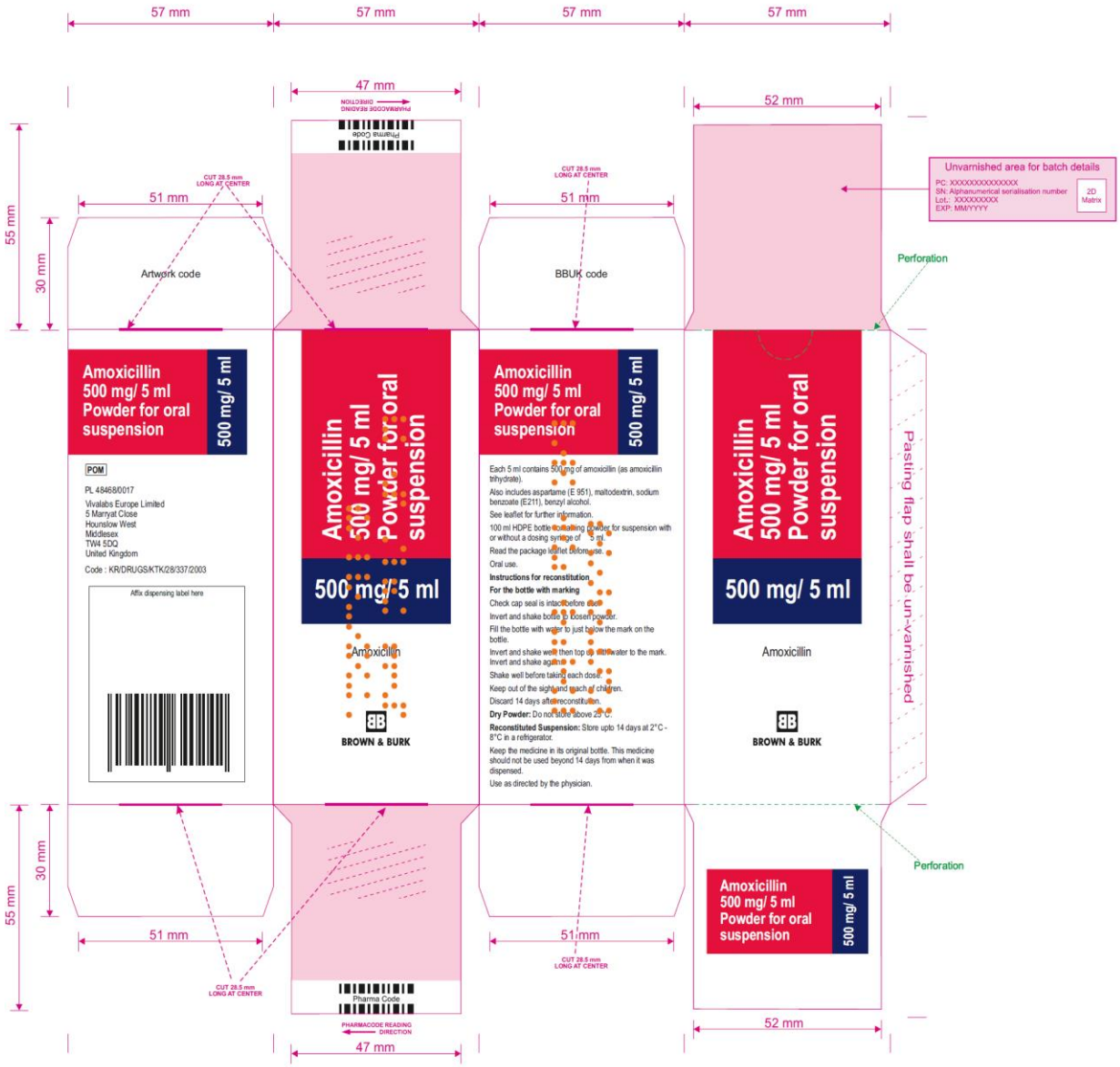

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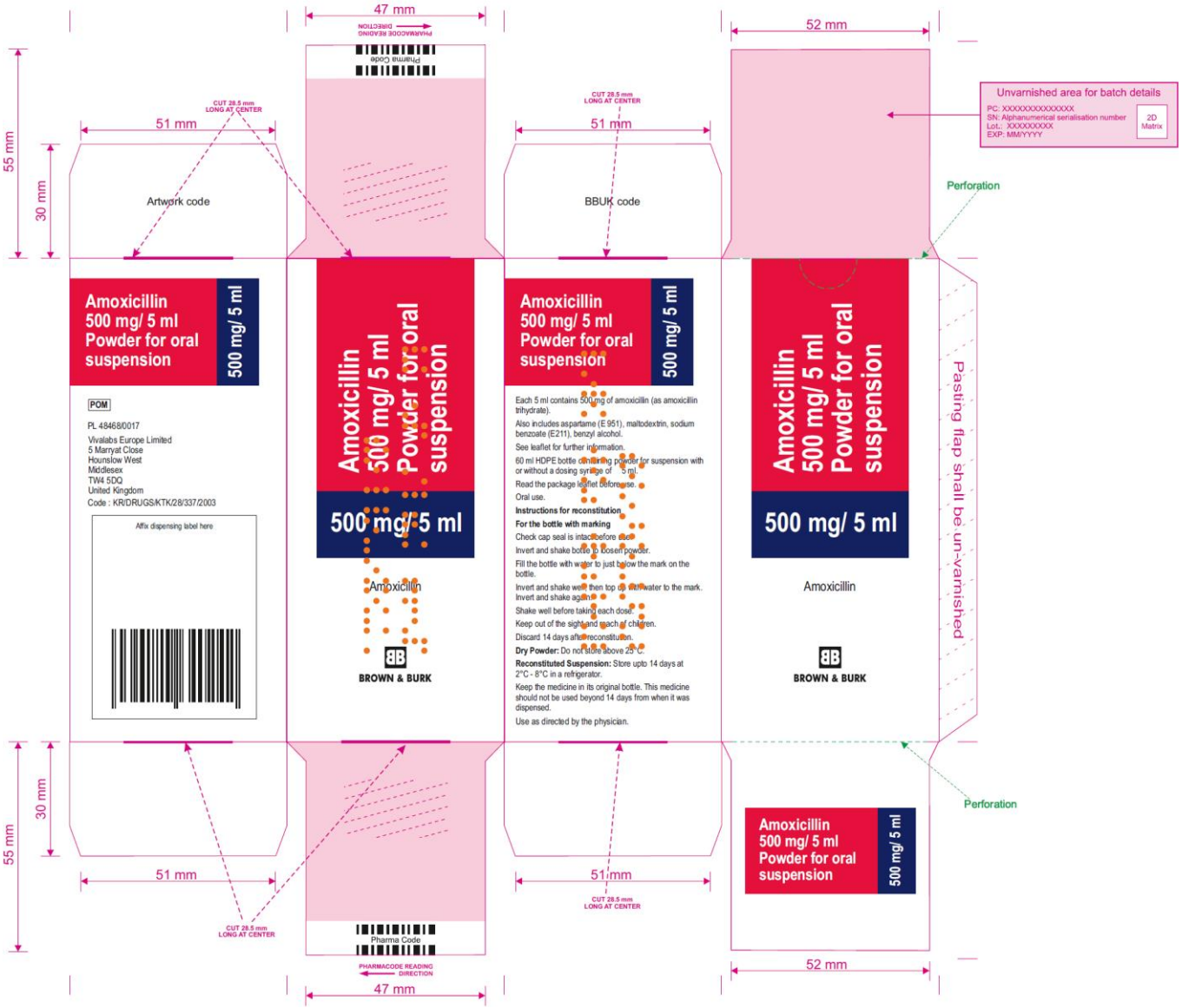
47 mm
52 mm
55 mm
30 mm
51 mm
Artwork code
BBUK code
Unvarnished area for batch details
PC: XXXXXXXXXXXXX
SN: Alphanumerical serialisation number
Lot.: XXXXXXXX
EXP: MM/YYYY
2D Matrix
Perforation
Amoxicillin 500 mg/ 5 ml Powder for oral suspension
500 mg/ 5 ml
POM
PL 48468/0017
Vivalabs Europe Limited
5 Marryat Close
Hounslow West
Middlesex
TW4 5DQ
United Kingdom
Code : KR/DRUGS/KTK/28/337/2003
Affix dispensing label here
Each 5 ml contains 500 mg of amoxicillin (as amoxicillin trihydrate).
Also includes aspartame (E 951), maltodextrin, sodium benzoate (E211), benzyl alcohol.
See leaflet for further information.
60 ml HDPE bottle containing powder for suspension with or without a dosing syringe of 5 ml.
Read the package leaflet before use.
Oral use.
Instructions for reconstitution
For the bottle with marking
Check cap seal is intact before use.
Invert and shake bottle to loosen powder.
Fill the bottle with water to just below the mark on the bottle.
Invert and shake well then top up with water to the mark.
Invert and shake again.
Shake well before taking each dose.
Keep out of the sight and reach of children.
Discard 14 days after reconstitution.
Dry Powder: Do not store above 25°C.
Reconstituted Suspension: Store upto 14 days at 2°C - 8°C in a refrigerator.
Keep the medicine in its original bottle. This medicine should not be used beyond 14 days from when it was dispensed.
Use as directed by the physician.
Amoxicillin
BROWN & BURK
Pasting flap shall be un-varnished
Perforation
Pharma Code
PHARMACODE READING DIRECTION
CUT 28.5 mm LONG AT CENTER


128 mm
65 mm
Amoxicillin
500 mg/ 5 ml Powder for oral suspension
500 mg/ 5 ml
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Hounslow West
Middlesex, TW4 5DQ
United Kingdom
PHARMACODE
PHARMACODE READING DIRECTION
Size: 128(L) x 65(W) mm
Unvarnish area for batch details
LOT:XXXXXXXXX
EXP: MM/YYYY
will be printed online


130 mm
45 mm
Amoxicillin 500 mg/ 5 ml Powder for oral suspension
500 mg/ 5 ml
Amoxicillin
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EXP: MM/YYYY
will be printed online

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N