



Public Assessment Report

**AMOXICILLIN 250MG CAPSULES
PL 21880/0001**

**AMOXICILLIN 500MG CAPSULES
PL 21880/0002**

UKPAR

Medreich Plc

LAY SUMMARY

Amoxicillin 250mg and 500mg Capsules
(amoxicillin (as the trihydrate), capsule, 250 mg and 500 mg)

This is a summary of the Public Assessment Report (PAR) for Amoxicillin 250mg Capsules (PL 21880/0001) and Amoxicillin 500mg Capsules (PL 21880/0002). It explains how Amoxicillin 250mg and 500mg Capsules were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Amoxicillin 250mg and 500mg Capsules.

For practical information about using Amoxicillin 250mg and 500mg Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Amoxicillin 250mg and 500mg Capsules and what are they used for?

Amoxicillin 250mg and 500mg Capsules are a 'generic medicine'. This means that Amoxicillin 250mg and 500mg Capsules are similar to a 'reference medicine' already authorised in the European Union (EU) called Amoxil Capsules 250mg and Amoxil Capsules 500mg (Beecham group plc).

This medicine is used to treat infections caused by bacteria in different parts of the body. Amoxicillin may also be used in combination with other medicines to treat stomach ulcers.

How do Amoxicillin 250mg and 500mg Capsules work?

The active ingredient, amoxicillin, is an antibiotic belonging to a group of medicines called 'penicillins' which work by interfering with the bacteria that causes infection.

How are Amoxicillin 250mg and 500mg Capsules used?

The pharmaceutical form of this medicine is a capsule and the route of administration is oral (by mouth).

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

- Do not chew the capsules. Swallow the capsules with water without opening capsule
- Space the doses evenly during the day, at least 4 hours apart.

The usual oral 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 the carer how much amoxicillin they 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

The usual dose of amoxicillin is 250 mg to 500 mg three times a day or 750 mg to 1 g every 12 hours, depending on the severity and type of infection

- Severe infections: 750 mg to 1 g three times a day
- Urinary tract infection: 3 g twice daily for one day
- Lyme disease (an infection spread by parasites called ticks): Isolated erythema migrans (early stage - red or pink circular rash): 4 g a day, Systemic manifestations (late stage – for more serious symptoms or when the disease spreads around the body): up to 6 g a day
- Stomach ulcers: one 750 mg or one 1 g dose twice a day for 7 days with other antibiotics and medicines to treat stomach ulcers
- To prevent heart infection during surgery: the dose will vary according to the type of surgery. Other medicines may also be given at the same time. The patient's doctor, pharmacist or nurse can give them more details.
- The maximum recommended dose is 6 g per day

Kidney problems

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

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

This medicine can only be obtained with a prescription.

What benefits of Amoxicillin 250mg and 500mg Capsules have been shown in studies?

Because Amoxicillin 250mg and 500mg Capsules are a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Amoxil Capsules 250mg and Amoxil Capsules 500mg (Beecham group plc). 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 250mg and 500mg Capsules?

Because Amoxicillin 250mg and 500mg Capsules are a generic medicine, their 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.

For the full list of all side effects reported with Amoxicillin 250mg and 500mg Capsules, see section 4 of the package leaflet available on the MHRA website.

Why were Amoxicillin 250mg and 500mg Capsules approved?

It was concluded that, in accordance with EU requirements, Amoxicillin 250mg and 500mg Capsules have been shown to have comparable quality and to be bioequivalent to Amoxil Capsules 500mg (Beecham group plc). Therefore, the MHRA decided that, as for Amoxil Capsules 500mg (Beecham group plc); 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 Amoxicillin 250mg and 500mg Capsules?

Safety information has been included in the Summary of Product Characteristics (SmPCs) and the package leaflet for Amoxicillin 250mg and 500mg Capsules 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 Amoxicillin 250mg and 500mg Capsules

The Marketing Authorisations for Amoxicillin 250mg and 500mg Capsules were granted in the UK on 11 September 2007.

The full PAR for Amoxicillin 250mg and 500mg Capsules follows this summary.

For more information about use of Amoxicillin 250mg and 500mg Capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2016.

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I INTRODUCTION

Please note that the below scientific discussion consists of the original assessment of the product licences, plus a summary of key post approval changes at the end of this introduction section to improve the accuracy of this Public Assessment Report.

Based on the review of the data on quality, safety and efficacy, the UK granted Medreich plc Marketing Authorisations for the medicinal products Amoxicillin 250mg Capsules (PL 21880/0001) and Amoxicillin 500mg Capsules (PL 21880/0002) on 11th September 2007. The products are prescription-only medicines.

These are two strengths of amoxicillin, submitted as abridged applications according to Article 10.1 (formerly 10.1(a)(iii)) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the original products Amoxil Capsules 250mg and Amoxil Capsules 500mg (Beecham group plc). The reference products have been authorised in the UK since April 1972 and so the 10-year period of data exclusivity has expired.

The products contain the active ingredient amoxicillin (as the trihydrate), a broad spectrum antibiotic. It is a derivative of ampicillin with a similar antibacterial spectrum including gram-positive, gram-negative and corinebacterium spp. Amoxicillin exerts its bactericidal action by interfering with the bacterial cell wall synthesis. Amoxicillin possesses the safety profile of a penicillin.

Amoxicillin 250mg Capsules and Amoxicillin 500mg Capsules are indicated for the treatment of infection: Amoxicillin is a broad spectrum antibiotic indicated for the treatment of following infections in adult and children (see sections 4.2, 4.4, and 5.1 of the SmPC):

- 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

Prophylaxis of endocarditis: Amoxicillin may be used for the prevention of bacteraemia associated with procedures such as dental extraction, in patients at risk of developing bacterial endocarditis.

Consideration should be given to official local guidance on the appropriate use of antibacterial agents. Susceptibility of the causative organism to the treatment should be tested (if possible), although the therapy may be initiated before the results are available.

These applications were submitted at the same time and the applicant presented two bioequivalence studies comparing the applicant's 250mg and 500mg products with the reference products Amoxil Capsules 250mg and Amoxil Capsules 500mg (Beecham group plc). The Scientific Discussion refers to both products.

Summary of key post-approval changes:

The following post-approval variations have been granted for these licences:

1. 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, as amended. The language used for the purpose of user testing the PIL 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. (PL 21880/0001 & 0002-0006)
2. The addition of a new pack size of 500 capsules granted on 14/02/2011 (PL 21880/0001-0021)
3. The registration of a new polypropylene container granted on 15/02/2011 (PL 21880/0001-17 and PL 21880/0002-0018)
4. The addition of a new pack size of 100 capsules granted on 15/02/2011 (PL 21880/0002-0022)
5. To register an additional pack size of 15 capsules to the currently approved pack sizes of 3, 6, 12, 21 and 50 tablets (PL 21880/0001 & 0002-0035).

II QUALITY ASPECTS

II.1 INTRODUCTION

Each capsule contains amoxicillin trihydrate equivalent to 250 mg or 500 mg amoxicillin. Other ingredients consist of pharmaceutical excipients, namely colloidal anhydrous silica, gelatin, tartrazine (E102), sunset yellow (E110), carmosine (E122), brilliant blue (E133), titanium dioxide (E171) and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

The capsules are packed in PVC / Aluminium blisters conforming to in-house specification. The blister strips are packaged with the PIL / SmPC into cardboard boxes. The product is packaged in sizes of 3, 6, 12, 21, and 50 capsules. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory.

All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with food.

II.2. DRUG SUBSTANCE

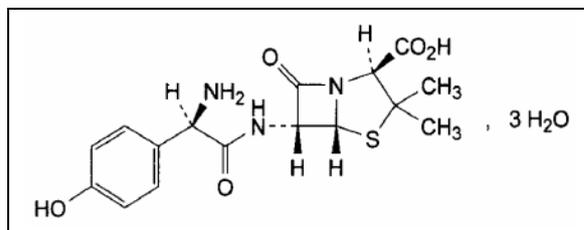
Amoxicillin trihydrate

Nomenclature:

INN: Amoxicillin trihydrate

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

Structure:



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

Molecular weight: 419.4

Physical form: White to off white crystalline powder

Solubility: 'Slightly soluble' in water and alcohol. Practically insoluble in ether and in fatty oils. Dissolves in dilute acids and dilute solutions of alkali hydroxides.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active amoxicillin trihydrate is stored in appropriate packaging, either a cropped polyethylene bag packed in a laminated bag or two polyethylene bags both cropped and packed in a fibre drum. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated for drug substance stored in the same immediate packaging as the commercial packaging, supporting a retest period of 60 months, with no specific storage instructions.

II.3. MEDICINAL PRODUCT

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of the gelatin capsules that comply with acceptable in-house specifications. Satisfactory certificates of analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is gelatin. Certificates of suitability have been provided by all the gelatin suppliers stating that the gelatin they provide meets the criteria described in the current version of the monograph 'Products with risk of transmitting agents of animal spongiform encephalopathies'.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Dissolution profiles for the drug product were found to be similar to those for the reference product.

The impurity profile for the drug product was marginally inferior to that of the reference product, but complied with the requirements of the proposed finished product specification.

Manufacture of the product

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory, and complies with the Ph. Eur. general monograph for capsules and the BP monograph for amoxicillin capsules. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. 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 capsules are packed in PVC / Aluminium blisters conforming to in-house specification. The blister strips are packaged with the PIL / SmPC into cardboard boxes. The product is packaged in sizes of 3, 6, 12, 21, and 50 capsules. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory.

All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with food.

Stability of the product

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are “Do not store above 25 degrees”, “Store in the original packaging”.

II.4 DISCUSSION ON CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL ASPECTS

It is recommended that Marketing Authorisations are granted for these applications.

Amoxicillin 250mg Capsules and Amoxicillin 500mg Capsules have been shown to be generic products of Amoxil Capsules 250mg and Amoxil Capsules 500mg respectively. The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance, pharmaceutical form and bioequivalence.

III NON-CLINICAL ASPECTS

These applications are for products claiming to be generic medicinal products of Amoxil Capsules 250mg and Amoxil Capsules 500mg (Beecham group plc), which have been licensed within the EEA for over 10 years.

No new non-clinical data have been supplied with these applications and none are required for applications of this type.

IV CLINICAL ASPECTS

IV.1 INTRODUCTION

INDICATIONS

Treatment of Infection: Amoxicillin is a broad spectrum antibiotic indicated for the treatment of commonly occurring bacterial infections such as:

Upper respiratory tract infections

Otitis Media

Acute and chronic bronchitis

Chronic bronchial sepsis

Lobar and bronchopneumonia

Cystitis, urethritis, pyelonephritis

Bacteriuria in pregnancy

Gynaecological infections including puerperal sepsis and septic abortion

Gonorrhoea

Peritonitis

Intra-abdominal sepsis

Septicaemia

Bacterial endocarditis

Typhoid and paratyphoid fever

Skin and soft tissue infections

Dental abscess (as an adjunct to surgical management)

Helicobacter pylori eradication in peptic (duodenal and gastric) ulcer disease.

In children with urinary tract infection the need for investigation should be considered.

Prophylaxis of endocarditis: Amoxicillin may be used for the prevention of bacteraemia associated with procedures such as dental extraction, in patients at risk of developing bacterial endocarditis.

The proposed indications are in line with those laid out in the SmPCs of the reference products.

Amoxicillin is rapidly absorbed when given orally. It is widely distributed and is reported to produce peak antibiotic plasma concentrations that are up to twice as high as those from the same dose of ampicillin.

The presence of food in the stomach does not appear to diminish absorption significantly.

Up to 20% is bound to plasma proteins in the circulation and plasma half-lives of about one hour have been reported. Amoxicillin diffuses across the placenta; little appears to be excreted in breast milk. It penetrates well into purulent and mucoid sputum and low concentrations have been found in ocular fluid. Concentrations of the

antibiotic have been detected in the CSF of patients with inflamed meninges when given intra-venously.

About 60% of an oral dose of Amoxicillin is excreted unchanged in the urine in 6 hours by glomerular filtration and tubular secretion. High concentrations have been reported in bile.

Amoxicillin inhibits side-wall synthesis in susceptible bacteria, but it is inactivated by penicillinase. Complete cross-resistance has been reported between Amoxicillin and Ampicillin.

IV.2 PHARMACOKINETICS

The applicant presents two bioequivalence studies (one for each strength). Although both trials have the same design and endpoints they will be described separately.

AMOX/2004/148:

This is a randomised, 2-treatment, 2-sequence, 2-period, 2-way crossover, single-dose bioequivalence study comparing two formulations of amoxicillin. The test product was Amoxicillin 250mg capsules (Medreich plc). The reference product was Amoxil capsules 250mg (Beecham group plc).

A total of 29 subjects were considered eligible from a total of 37 males screened. Twenty eight of those were enrolled, 26 completed the cross-over study, but only 24 were used for the analysis of the data. According to the EU guidance note on bioequivalence studies “the number of subjects required is determined by the error variance associated with the primary characteristics to be studied (as estimated from pilot experiment, from previous studies or from published data), by the significance level (0.05) desired, and by the deviation from the reference product compatible with bioequivalence and with safety and efficacy”.

Medreich have previously conducted a bioequivalence study of Amoxicillin and used its data for the sample size calculations. From this study they showed that for Amoxi-Clav 250/125 mg Amoxicillin/Clavulanic Acid Tablets, AUC(0-t) of Amoxicillin (250mg) has inter-subject variability %CV of 20.0.

In this previous study the protocol specified that the data for 24 subjects would be reported. This was based on a bioequivalence range of 80% to 125% for AUC and C_{max} , within subject % CV of 19%, and a test / reference mean ratio between 0.95 and 1.05. Therefore, more than 20 subjects were needed to achieve a power of 80% to show bioequivalence.

Although the clinical part of the study was completed for 26 subjects, samples of only 24 subjects were analysed and reported as per the protocol. Bioanalysis was not performed for the extra 2 subjects which was not required as per the protocol.

Study subjects received both products sequentially (washout period was 7 days) in a randomised fashion, under fasting conditions. All other conditions (medicines, diet, exercise, etc...) were standardised as well. Blood samples were taken pre-dosing and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 10 hours post-dosing. Safety evaluations included pre and post dosing haematological and clinical chemistry, as well as

collection of AE. Drug concentration measurements were performed using HPLC-Fluorescence method, LOQ was reported at 0.20µg/mL.

The following pharmacokinetic variables were calculated individually and as a group for each product: C_{max} , T_{max} , $T_{1/2}$, Kel , AUC_{0-t} and $AUC_{0-\infty}$. Ratios of test/reference mean product were expressed as point estimates of relative bioavailability. ANOVA test was performed on C_{max} , AUC_{0-t} , $AUC_{0-\infty}$ and $T_{1/2}$ using Latin square design. A non-parametric test (Kruskal Wallis) was used to compare T_{max} values.

Data and results were evaluated and statistical analysis was performed.

No protocol deviations were reported.

The results are summarised below.

Table 1. Summary of pharmacokinetic parameters

Parameter	Test product	Reference product
	Mean (SD)	Mean (SD)
C_{max} (µg/ml)	3.549 (±1.20)	3.513 (±1.24)
T_{max} (h)	2.042 (±0.72)	2.125 (±1.02)
AUC_{0-t} (µg.h/ml)	12.422 (±3.57)	12.239 (±3.85)
$AUC_{0-\infty}$ (µg.h/ml)	15.041 (±8.69)	13.236 (±4.01)
$T_{1/2}$ (h)	4.792 (±1.82)	2.076 (±0.52)

Note: all p-values were >0.05

Table 2. Summary of comparative bioavailability

Parameter (untransformed)	Mean ration (A/B)	90%CI	
		Lower	Upper
C_{max}	1.103	0.9099	1.1701
AUC_{0-t}	1.054	0.9454	1.1092
$AUC_{0-\infty}$	1.208	0.9624	1.2428

Subject 3 was noted to have very high values for $t_{1/2}$ and $AUC_{0-\infty}$ and considered to be an outlier. Re-analysis of the data was performed, excluding the results for Subject 3. This did not change the conclusion of the study, i.e. that the formulations are still bioequivalent. The recalculated point estimate and 90% CI for the C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ lie within the 0.8-1.25 acceptance limits. This is acceptable.

The applicant summarises the results and conclusions as follows:

- The main pharmacokinetic criteria for bioequivalence (ratios of test/reference of C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$) were met, hence the test formulation was deemed to be equivalent to the reference product.
- No statistically significant difference was found when comparing the means of C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{max} and $T_{1/2}$.
- A significant subject effect was observed in all parameters except for T_{max} .
- A total of 4 AE were recorded, all mild and unlikely to be related to the test product. There is no clinical relevance to the subject effect seen as statistically significant. Subject effect in crossover pharmacokinetic studies reflects intrasubject variability of the investigational compound. This does not affect

the final conclusion over bioequivalence. The use of Confidence Intervals which provides the range of values based on the sample data is much more informative and meaningful.

AMOX/2004/149:

This is also a randomised, 2-treatment, 2-sequence, 2-period, 2-way crossover, single-dose bioequivalence study comparing two formulations of amoxicillin. The test product was Amoxicillin 500mg capsules (Medreich plc). The reference product was Amoxil capsules 500mg (Beecham group plc).

The sample size was calculated as 18 to 20 subjects based on a previous study. A total of 30 subjects were considered eligible from a total of 33 males screened. Twenty eight of those were enrolled, 27 completed the cross-over study, but only 24 were used for the analysis of the data. Study subjects received both products sequentially (washout period was 7 days) in a randomised fashion, under fasting conditions. All other conditions (medicines, diet, exercise, etc...) were standardised as well. Blood samples were taken pre-dosing and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 10 hours post-dosing. Safety evaluations included pre and post dosing haematological and clinical chemistry, as well as collection of AE. Drug concentration measurements were performed using HPLC-Fluorescence method, LOQ was reported at 0.198µg/mL.

The following pharmacokinetic variables were calculated individually and as a group for each product: C_{max} , T_{max} , $T_{1/2}$, Kel , AUC_{0-t} and $AUC_{0-\infty}$. Ratios of test/reference mean product were expressed as point estimates of relative bioavailability. ANOVA test was performed on C_{max} , AUC_{0-t} , $AUC_{0-\infty}$ and $T_{1/2}$ using Latin square design. A non-parametric test (Kruskal Wallis) was used to compare T_{max} values.

Data and results were evaluated and statistical analysis was performed.

No protocol deviations were reported.

The results are summarised below.

Table 1. Summary of pharmacokinetic parameters

Parameter	Test product	Reference product
	Mean (SD)	Mean (SD)
C_{max} (µg/ml)	6.314 (±1.96)	6.422 (±1.91)
T_{max} (h)	2.542 (±0.99)	2.521 (±1.17)
AUC_{0-t} (µg.h/ml)	25.117 (±5.50)	23.854 (±5.49)
$AUC_{0-\infty}$ (µg.h/ml)	27.317 (±6.57)	25.408 (±5.58)
$T_{1/2}$ (h)	4.250 (±1.65)	2.137 (±0.50)

Note: p-values were all >0.05

Table 2. Summary of comparative bioavailability

Parameter (untransformed)	Mean ration (A/B)	90% CI	
		Lower	Upper
C_{max}	0.981	0.8709	1.105
AUC_{0-t}	1.058	0.9785	1.1431
$AUC_{0-\infty}$	1.073	0.9947	1.158

The applicant summarises the results and conclusions as follows:

- The main pharmacokinetic criteria for bioequivalence (ratios of test/reference product of C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$) were met, hence the test formulation was deemed to be equivalent to the reference product.
- No statistically significant difference was found when comparing the means of C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{max} and $T_{1/2}$.
- A significant subject effect was observed in AUC_{0-t} , and $AUC_{0-\infty}$.
- A total of 4 AE were recorded, all mild and unlikely to be related to the test product. The subject effect observed has no implications on clinical efficacy or safety of the test product. Subject effect in crossover pharmacokinetic studies reflects intrasubject variability of the investigational compound. This does not affect the final conclusion over bioequivalence. It is considered that the CI gives a more informative picture of clinical efficacy.

Overall conclusions on pharmacokinetics

The bioequivalence studies supporting the claim of the test products to be generic medicinal products of the reference products are of adequate design. The bioequivalence of the test and reference products was shown with 90%CI within the 0.8-1.25 acceptance limits.

IV.3 PHARMACODYNAMICS

Effectively, the pharmacodynamics of amoxicillin relate to its antibacterial activity. There are no new data presented by the applicant.

IV.4 CLINICAL EFFICACY

Efficacy is reviewed in the Clinical Expert Report. The reference products are established and the applications depend upon the ability to show bioequivalence with the reference products.

Amoxicillin is one of the most widely prescribed antibiotics and its efficacy is well recognised.

IV.5 CLINICAL SAFETY

Safety is reviewed in the Clinical Expert Report.

Amoxicillin is a very well established, widely used, and well tolerated drug.

EXPERT REPORT

The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS

The proposed SmPCs have been brought into line with those for the reference products and are satisfactory.

PATIENT INFORMATION LEAFLET

The PIL is in line with the approved SmPCs and is satisfactory.

LABELLING

The labelling is satisfactory.

IV.6 DISCUSSION ON THE CLINICAL ASPECTS

All issues have been adequately addressed by the applicant. The bioequivalence of the test and reference products was shown with 90% Confidence Intervals within general acceptance limits. The SPCs and PIL of the test products are in line with the SmPCs and PIL of the reference products. Marketing authorisations should be granted for these products.

V OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Amoxicillin 250mg Capsules and Amoxicillin 500mg Capsules 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

Bioequivalence has been demonstrated between the applicant's Amoxicillin 250mg Capsules and Amoxicillin 500mg Capsules, and their respective reference products Amoxil Capsules 250mg and Amoxil Capsules 500mg (Beecham group plc).

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with that for Amoxil Capsules 250mg and Amoxil Capsules 500mg.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Amoxicillin is a very well established, widely used, and well tolerated drug which has been available in the UK for over thirty years. Extensive clinical experience is considered to have demonstrated the therapeutic value of the compound. The only concerns regarding its use have been in terms of appropriate antibiotic prescribing in order to reduce the spread of antibiotic resistance. The risk benefit is, therefore, considered to be positive.

**AMOXICILLIN 250MG CAPSULES
PL 21880/0001**

**AMOXICILLIN 500MG CAPSULES
PL 21880/0002**

Steps Taken After Initial Procedure - Summary

The following table lists non-urgent safety updates to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

Date submitted	Application type	Scope	Outcome
12/10/2007	PIU label	The design of the carton label for Amoxicillin 250mg Capsules and Amoxicillin 500mg Capsules has been changed, with no textual changes. This is for pack size 21 only.	Application granted 15/10/2007
11/03/2016	Type 1B	PL 21880/0001-0067 & PL 21880/0002-0067: To update sections 2, 4.6, 4.8 and of the SmPC in line with the QRD template and sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.2, 5.3 of the SmPC in line with the brand leader. Consequently the leaflet has been updated.	Approved 03/06/2016-see Annex 1.

ANNEX 1

Our Reference:	PL 21880/0001-0067 PL 21880/0002-0067
Product:	Amoxicillin 250 mg Capsules Amoxicillin 500 mg Capsules
Marketing Authorisation Holder:	Medreich Plc
Active Ingredient(s):	Amoxicillin trihydrate
Type of Procedure:	National
Submission Type:	Variation
Submission Category:	Type IB
Submission Complexity:	Standard
EU Procedure Number (if applicable):	Not applicable

Reason:

To update sections 2, 4.6, 4.8 and of the SmPC in line with the QRD template and sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.2, 5.3 of the SmPC in line with the brand leader. Consequently the leaflet has been updated.

Supporting Evidence

Revised SmPC fragments and PIL.

Evaluation

The proposed changes to the SmPCs and PIL are in line with the reference product. The updated SmPC fragments and PIL have been incorporated into the Marketing Authorisations.

Conclusion

The proposed changes to the SmPCs and PIL are acceptable.

Decision - Approved on 03 June 2016.

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 current approved labelling Amoxicillin 250mg and 500mg Capsules is as follows:

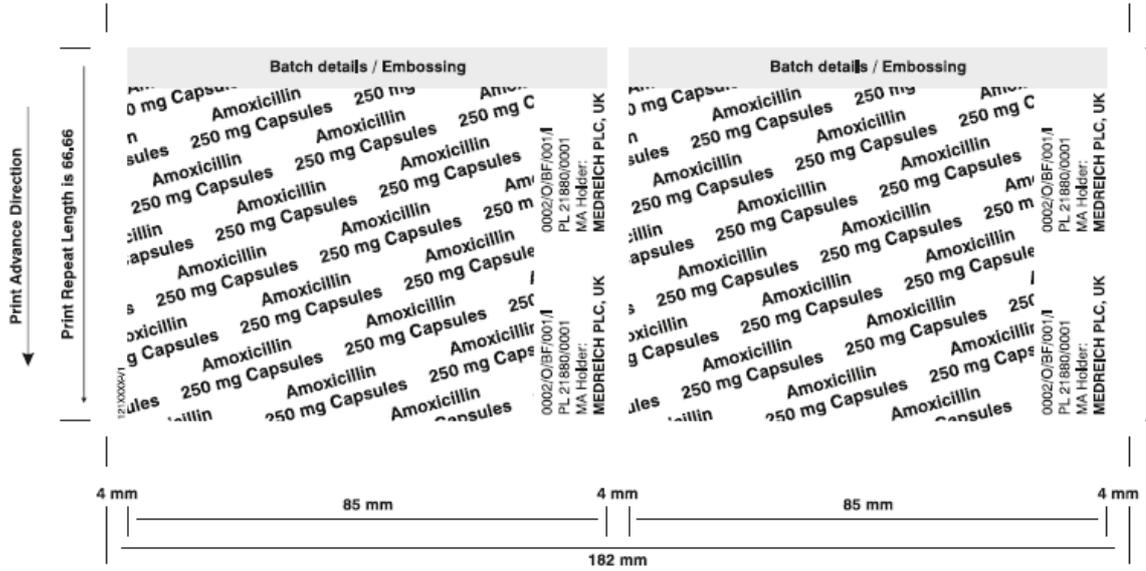


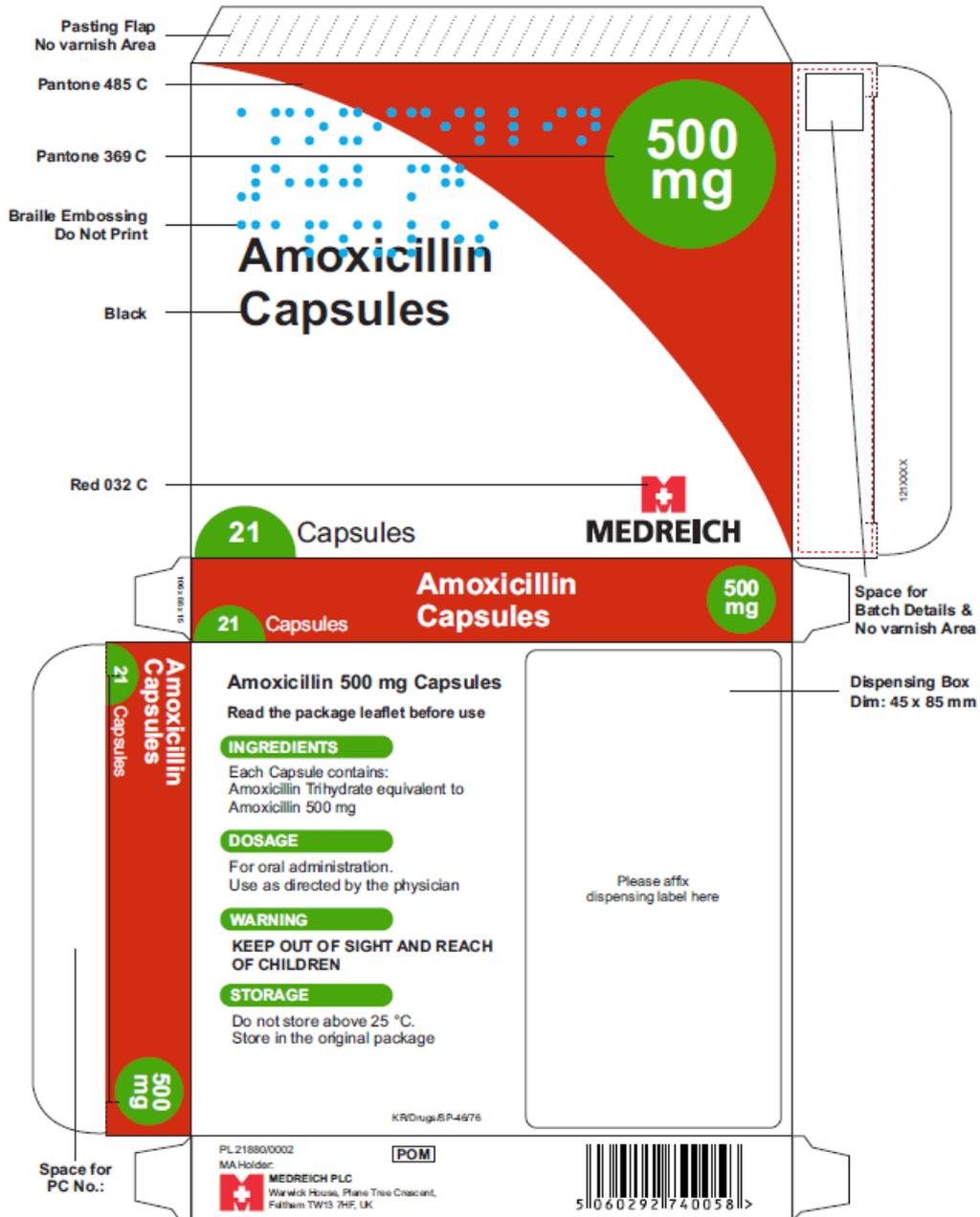
Braille Reads:-

amoxicillin

#250 mg

capsules



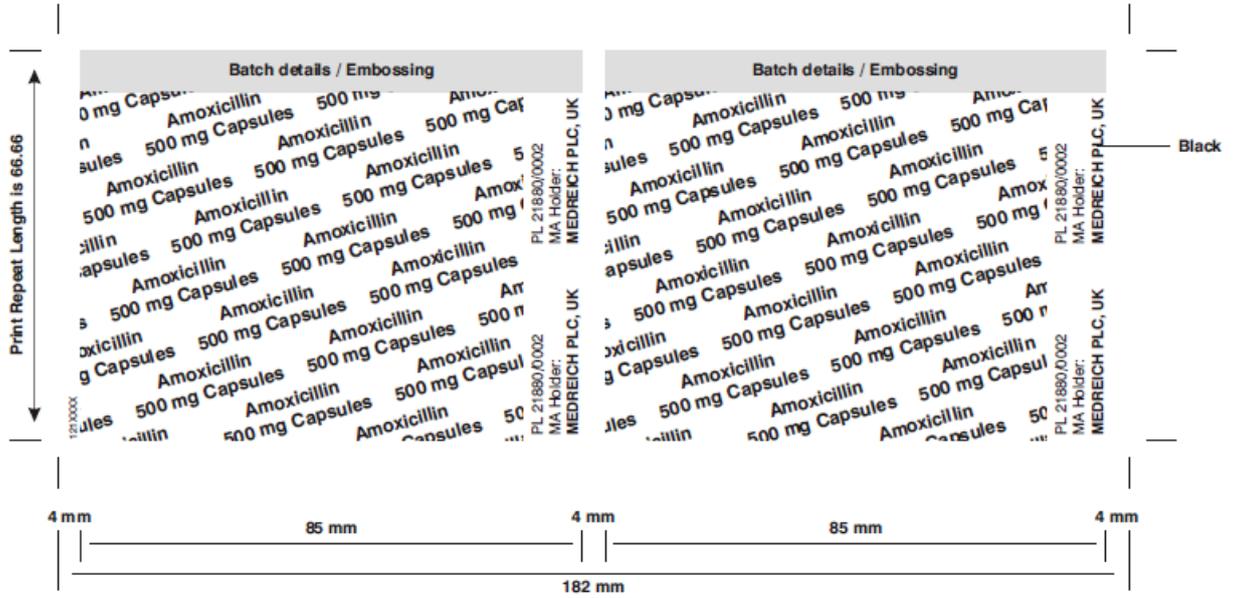


Braille Reads:

amoxicillin

#500 mg

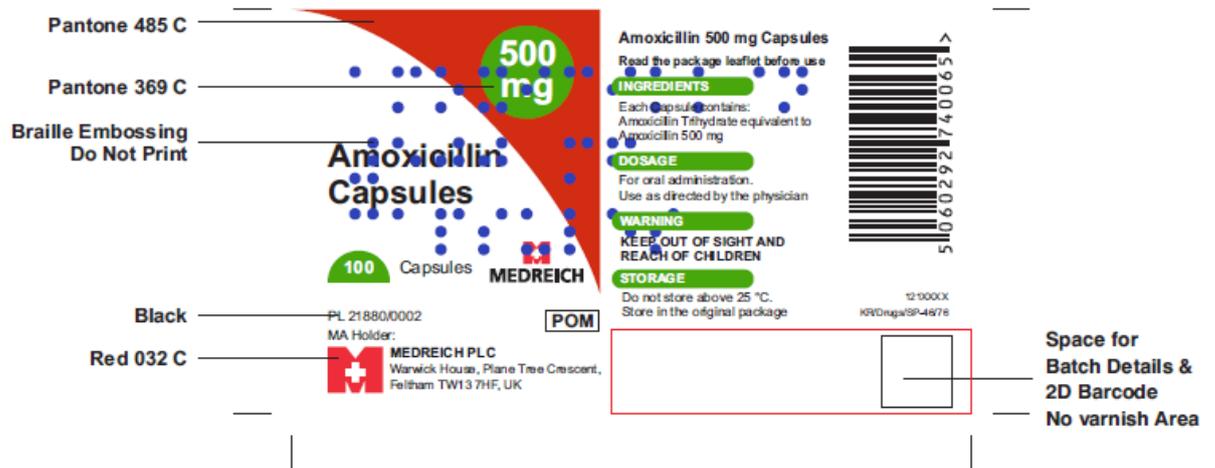
capsules



Container:



Braille Reads:
Amoxicillin
250mg
Capsules



Braille Reads:
Amoxicillin
500mg
Capsules

