PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Amoxicilline disper 500/750/1000, dispersible tablets 500, 750, and 1000 mg
Sandoz B.V., the Netherlands

amoxicillin (as trihydrate)

Pharmacotherapeutic group: ß-Lactam antibacterials, penicillins with extended spectrum
ATC code: J01CA04
Route of administration: oral
Therapeutic indication: oral treatment of bacterial infections caused by amoxicillin-susceptible gram-positive and gram-negative pathogens.
Prescription status: prescription only
Date of first authorisation in NL: 17 July 2006
Concerned Member States: Mutual recognition procedure with FI (only 500 and 750 mg, both strengths were withdrawn in FI on 19 August 2008) ES (only 750 and 1000 mg), and PL

Application type/legal basis: Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Amoxicilline dispers 500/750/1000, dispersible tablets 500, 750, and 1000 mg, from Sandoz B.V. The date of authorisation was on 17 July 2006 in the Netherlands.

The product is indicated for oral treatment of the following bacterial infections caused by amoxicillin-susceptible gram-positive and gram-negative pathogens:

- Infections of the upper respiratory tract, including infections of the ears, nose and throat: acute otitis media, acute sinusitis and bacterial pharyngitis
- Infections of the lower respiratory tract: acute exacerbation of chronic bronchitis, community-acquired pneumonia
- Infections of the lower urinary tract: cystitis,
- Prophylaxis of endocarditis in patients at risk i.e. surgery in the oral cavity or upper airways.

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

A comprehensive description of the indications and posology is given in the SPC.

Amoxicillin is an aminobenzyl penicillin that has a bactericidal action due to its inhibition of the synthesis of the bacterial cell wall.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Clamoxyl Duodispers 500/750/1000 mg, which has been registered in France by SmithKline Beecham B.V. The historical reference product Clamoxyl Duodispers 500/750/1000 mg tablets (GlaxoSmithKline, the Netherlands) was authorized in the Netherlands on 1979 (500 and 1000 mg tablets, NL license RVG 08297 & 08298) and 1975 (750 mg tablets, NL license RVG 06700) and has been withdrawn for commercial reasons on 31 December 2005. In addition, reference is made to Clamoxyl Duodispers authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Clamoxyl 1000 mg tablets, registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted.
II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is amoxicillin trihydrate, an established active substance described in the European Pharmacopoeia (Ph. Eur.*). The substance is structurally related to other penicillines, is a crystalline white powder and is slightly soluble in water. Polymorphism has not been observed. Particle size of the substance is not an issue, considering the dosage form: dispersible tablets and also the rapid dissolution of the product if swallowed without first dispersing the tablet.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacture
The manufacturing process has been sufficiently described and validated.

Quality control of drug substance
The drug substance specification has been established in-house in line with the CEP and is considered acceptable. Batch-to-batch consistency of manufacturing of the substance according to the specification has been evaluated by the EDQM.

Stability
Stability data on the active substance have been provided for six batches stored at 25-30°C (= “non-ICH” conditions) during 60 months and six months at 40°C/75% RH. Taking into consideration that also additional studies have been performed to study moisture sensitivity with favourable results, the deviation regarding temperature and humidity of the formal studies at real time conditions can be considered acceptable. The batches were stored in the approved packaging. The results of the stability studies justify the claimed retest period and storage condition: 5 years, store below 30°C.

* Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.
Medicinal Product

Composition
Amoxicillin trihydrate is the main component, taking account of ≈ 80% of the tablet mass: the product contains 574.0 mg amoxicillin trihydrate equivalent with 500 mg amoxicillin, 861 mg amoxicillin trihydrate equivalent with 750 mg amoxicillin and 1148 mg amoxicillin trihydrate equivalent with 1000 mg amoxicillin, respectively. The tablets contain score lines. The tablets can be easily broken by hand.

The dispersible tablets are packed in PVC/PVDC/Al blisters (transparent).

The excipients are: peach-apricot flavouring (powdered), orange flavouring (powdered), magnesium, stearate (E470b), aspartame (E951), croscarmellose sodium, mannitol (E421), talcum (E553b), colloidal silicon dioxide (E551), microcrystalline cellulose (E460), maltodextrin, soluble starch, and titanium dioxide (E171).

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients and packaging are usual for this type of dosage form. The MAH has justified the use and amounts of excipients by studying different types and amounts of excipients. In conclusion, the presented results show that the MAH has committed to the methodology of the Note for Guidance on Development pharmaceutics and that the specifications of the finished product will be met and that the finished product is of good quality. The pharmaceutical development of the product has been adequately performed.

The aim was that the tablets should be dispersed quickly in the dissolving medium or be swallowed directly. Because of the direct swallowing the tablets have been covered by a coating.

The biobatch used in the Bioequivalence study has been provided. Bioavailability was performed against Clamoxyl Dispersible 1000 mg, the innovator product from the French market. This product can be considered representative for innovators of all EU countries, considering the type of dosage form and the rapid dissolution: after approx. 20 minutes 100% is dissolved. It has been demonstrated that the dissolution of the tablet halves is comparable with the dissolution of the complete tablets.

Excipients
The excipients comply with the Ph.Eur. except the flavourings, for which in-house specifications have been submitted. Soluble starch complies with both the Ph.Eur. and an in-house specification. All these specifications are acceptable.

Manufacturing process
The method of preparation refers to a conventional standard procedure involving the following steps: wet granulation with water, subsequent drying, sieving, regranulation of the fine portion, mixing, tabletting, coating (aqueous suspension) and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for at least three batches (pilot and commercial) of per tablet strength. The product is manufactured using conventional manufacturing techniques. The three tablet strengths are fully dose proportional.

Quality control of drug product
The product specification includes tests for fill in appearance, identity, assay, degradation, water, uniformity of dosage units, microbiological purity, fineness of dispersion, dissolution. The release and shelf-life limits are identical with the exception of assay and partially regarding degradation products. The limits are acceptable. The analytical methods have been adequately described and validated. Batch analytical data of at least three production batches per strength have been provided from the proposed production site, demonstrating compliance with the release specification.

Stability tests on the finished product
Stability data on the product have been provided for a great amount of pilot batches and production batches of the different tablet strengths, stored during 36 months at 25°C/60% RH, six months at 40°C/75% RH, 30°C/60% RH and 30°C/70% RH. The conditions used in the stability studies are
according to the ICH stability guideline. The batches were stored in the proposed packaging: (transparent) PVC/PVDC/Aluminium blister. Based on the results submitted, a shelf-life of three years with storage condition “store below 25°C store in the original package in order to protect from moisture” is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a generic formulation of Clamoxyl Duodispers, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of amoxicillin released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Amoxicillin is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Amoxicillin disper 1000 dispersible tablets 1000 mg (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Clamoxyl 1000 mg tablets (SmithKline Beecham, France).

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Study design

A single center, open, randomized, two-way, crossover bioequivalence study was carried out under fasted conditions in 22 healthy (11 male, 11 female) volunteers, aged 19-38 years. Each subject received a single dose (1000 mg) of one of the 2 amoxicillin formulations. The tablets were orally administered with 240 ml water after a 10 h fasting period. For each subject there were 2 dosing periods, separated by a washout period of 9 days. Blood samples were collected predose and at 0.25, 0.50, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, and 10 hours after administration of the products.

The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Amoxicillin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of amoxicillin. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.
Results
All 22 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ (median, range)) of amoxicillin under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$ µg.h/ml</th>
<th>$\text{AUC}_{0-\infty}$ µg.h/ml</th>
<th>$C_{\text{max}}$ µg/ml</th>
<th>$t_{\text{max}}$ h</th>
<th>$t_{1/2}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>38.9 ± 9.1</td>
<td>40.8 ± 9.1</td>
<td>12.1 ± 3.8</td>
<td>2.0 (0.75 – 3.0)</td>
<td>1.2 ± 0.3</td>
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<tr>
<td>Reference</td>
<td>37.9 ± 7.4</td>
<td>39.6 ± 7.4</td>
<td>12.1 ± 3.0</td>
<td>1.68 (1.0 – 5.0)</td>
<td>1.2 ± 0.3</td>
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<tr>
<td>*Ratio (90% CI)</td>
<td>1.01 (0.95 - 1.08)</td>
<td>1.02 (0.96 - 1.09)</td>
<td>0.99 (0.91 - 1.06)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>CV (%)</td>
<td>11.6</td>
<td>11.9</td>
<td>14.7</td>
<td>---</td>
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</tr>
</tbody>
</table>

*AUC$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
*AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
*C$_{\text{max}}$ maximum plasma concentration
*t$_{\text{max}}$ time for maximum concentration
*t$_{1/2}$ half-life

*ln-transformed values

The 90% confidence intervals calculated for $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of amoxicillin under fasted conditions, it can be concluded that Amoxicillin dispers 1000 dispersible tablets 1000 mg tablets and Clamoxyl 1000 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 500 and 750 mg tablets are dose proportional with the 1000 mg tablets. The results of the bioequivalence study performed with the 1000 mg tablets therefore apply to the other strengths.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Amoxicillin was first approved in 1972, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of amoxicillin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post-authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.
Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for Amoxicillin dispersible tablets marketed by Sandoz GmbH (procedure NL/H/0455/001-003/E/001).

Readability test
The texts are identical to the texts of procedure NL/0455/001-003, for which bridging was justified. A description of the assessment of the bridging of these texts are provided below.

The Amoxicillin disper leaflet has been bridged with Cruciol powder for oral suspension leaflet. A focused user test on the Amoxicillin disper leaflet has been performed. The focused user test was a supplement to the main user test conducted for the Cruciol leaflet. The choice for a focused user test was based on the inclusion of text in the Amoxicillin disper leaflet, which slightly differs from the text in the Cruciol leaflet.

Prior to the focused user test, three key points were defined, concerning specific safety and compliance issues for Amoxicillin disper.

Two focused user tests were performed, both were diagnostic. This is acceptable, because the aim of the focused user test was to investigate the ability of the respondents to find and to understand the information given in the leaflet.

Both focused user tests were performed with 10 participants. An even spread of ages ranging from 22 up to 61 years, an even proportion of both genders and an equally balanced educational level were taken into account when recruiting the respondents.

The tests confirmed that 90% of the participants were able to find each point of information. 90% of these participants were able to express the information correctly in their own words. It was therefore concluded that the leaflet fulfils the requirements of the regulatory authorities.

In addition to the quantitative outcome, participants also gave their qualitative feedback on the leaflet, concerning layout and language used in the leaflet. The leaflet contains several terms that appear to be difficult to understand for the average layperson.

It was therefore recommended that higher register, biomedical terms should be rewritten in everyday, layperson’s language where possible to improve readability of the leaflet.

The Cruciol readability report and the Cruciol leaflet were provided by the MAH. Comparing the Cruciol leaflet with the proposed leaflet for Amoxicillin disper lead to the conclusion that bridging was justified. The RMS further proposed to amendment in section Take special care with Amoxicillin disper (addition of...if you.) and reformulation of ‘This medicine...the infant’ in section Pregnancy and breast-feeding into a more patient friendly term. These proposals were implemented.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Amoxicilline disper 500/750/1000, dispersible tablets 500, 750, and 1000 mg have a proven chemical-pharmaceutical quality and are a generic form of Clamoxyl Duodispers 500/750/1000 mg tablets. Clamoxyl Duodispers is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for Amoxicilllin dispersible tablets marketed by Sandoz GmbH (NL/H/0455/001-003/E/001). The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Amoxicilline disper 500/750/1000 mg tablets were authorised in the Netherlands on 17 July 2006.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Amoxicilline disper 500/750/1000 dispersible tablets 500, 750 and 1000 mg with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 28 May 2008.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from May 2008 to May 2011.

The date for the first renewal will be: 28 May 2013.

The following post-approval commitments made during the procedure:

SPC:
The MAH has committed to submit immediately after the MRP a type II variation on SPC and PIL, with the same content as the variation for NL/H/0455/001-003/II/15. This commitment has been fulfilled, see variation NL/H/0914/001-003/II/001 in the ‘steps taken after the finalisation of the initial procedure’ table.
List of abbreviations

ASMF    Active Substance Master File
ATC     Anatomical Therapeutic Chemical classification
AUC     Area Under the Curve
BP      British Pharmacopoeia
CEP     Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP    Committee for Medicinal Products for Human Use
CI      Confidence Interval
C_max   Maximum plasma concentration
CMD(h)  Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV      Coefficient of Variation
EDMF    European Drug Master File
EDQM    European Directorate for the Quality of Medicines
EU      European Union
GCP     Good Clinical Practice
GLP     Good Laboratory Practice
GMP     Good Manufacturing Practice
ICH     International Conference of Harmonisation
MAH     Marketing Authorisation Holder
MEB     Medicines Evaluation Board in the Netherlands
OTC     Over The Counter (to be supplied without prescription)
PAR     Public Assessment Report
Ph.Eur. European Pharmacopoeia
PIL     Package Leaflet
PSUR    Periodic Safety Update Report
SD      Standard Deviation
SPC     Summary of Product Characteristics
t_1/2   Half-life
t_max   Time for maximum concentration
TSE     Transmissible Spongiform Encephalopathy
USP     Pharmacopoeia in the United States
## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
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<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
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<td>Withdrawal of the marketing authorization in FI on 19 August 2008.</td>
<td>NL/H/0914/001-002/MR</td>
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<td>26-9-2008</td>
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<td>3-4-2009</td>
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<td>7-8-2009</td>
<td>6-10-2009</td>
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<td>NL/H/0914/001-003/IA/008</td>
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