

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Azithromycine Mylan 250 mg and 500 mg film-coated tablets
Mylan B.V., the Netherlands**

azithromycin (as monohydrate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/1206/001-002/MR
Registration number in the Netherlands: RVG 29676-29677**

11 May 2010

Pharmacotherapeutic group:	antibacterials for systemic use, macrolides
ATC code:	J01FA10
Route of administration:	oral
Therapeutic indication:	bacterial infections induced by micro-organisms sensitive to azithromycin (see next page)
Prescription status:	prescription only
Date of first authorisation in NL:	26 September 2005
Concerned Member States:	Mutual recognition procedure with BE, DE, ES, FI, HU, MT, PL, SE, UK; IE (250 mg only); AT, CZ, DK, IT, NO, PT, SK (500 mg only)
Application type/legal basis:	Directive 2001/83/EC, Article 10(1), 10(3)

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 Azitromycine Mylan 250 mg and 500 mg film-coated tablets from Mylan B.V. The date of authorisation was on 26 September 2005 in the Netherlands.

The product is indicated for the following bacterial infections induced by micro-organisms sensitive to azithromycin:

- Infections of the lower respiratory tract: acute bronchitis and mild to moderate community-acquired pneumonia
- Infections of the upper respiratory tract: sinusitis and pharyngitis/tonsillitis
- Acute otitis media
- Infections of the skin and soft tissues of mild to moderate severity e.g. folliculitis, cellulitis, erysipelas
- Uncomplicated *Chlamydia trachomatis* urethritis and cervicitis.

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

Azithromycin is not the first choice for the empirical treatment of infections in areas where the prevalence of resistant isolates is 10% or more

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

Azithromycin is an azalide, a sub-class of the macrolid antibiotics. By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented. For azithromycin the AUC/MIC is the major PK/PD parameter correlating best with the efficacy of azithromycin. Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.

Complete cross resistance exists among *Streptococcus pneumoniae*, *betahaemolytic streptococcus* of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including *methicillin resistant S. aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Azithromax 250 mg and 500 mg film-coated tablets which have been registered in Sweden by Pfizer since 2 August 1995. In the Netherlands, Zithromax 250 mg and 500 mg tablets (NL License RVG 19432-19433) have been registered since 21 May 1997. In addition, reference is made to Azithromax authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. For Malta this is a hybrid application based on article 10(3), as only a different strength (250 mg) has been registered, as well as a different but comparable pharmaceutical form (capsules).

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 Azithromax 500 mg tablets, registered in Italy. 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 products.

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, as this is not required for a generic application.

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 these product types 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 azithromycin monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Azithromycin monohydrate is a fermentation product and appears as a white or almost white powder. The macrolide nucleus comprises 10 chiral carbon atoms, the side units desosaminy and cladinoyl possess each 4 chiral centers. No different polymorphic forms are described for azithromycin monohydrate.

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.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The MAH has provided his own specification, including general Ph.Eur. requirements, the additional requirements stated in the CEP and additional microbial purity, particle size and residual solvents.

Stability of drug substance

The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** 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

Azithromycin Mylan 250 mg is a white to off-white, elongated tablet, unmarked on its sides.

Azithromycin Mylan 500 mg is a white to off-white, elongated tablet with a deep groove on one side and a dividing line on the other side. The tablet can be divided into equal doses.

The film-coated tablets are packed in PVC/PVDC/aluminium blister packs.

The excipients are:

Tablet core - microcrystalline cellulose (E460), pregelatinised starch (maize starch), sodium starch glycolate (Type A), anhydrous colloidal silica (E551), sodium lauryl sulphate, magnesium stearate (E470b)
Film coating - polyvinyl alcohol ((partially hydrolysed), titanium dioxide (E171), talc (E553b), soya lecithin, xanthan gum (E415).

The two strengths are completely dose proportional.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The packaging is usual and suitable for the product at issue.

The drug formulation development has been sufficiently described, discussing conversion studies and equilibrium moisture studies, and after that the dissolution profiles were compared to the innovator. The comparative dissolution profiles of innovator batches from Sweden, Austria, the Netherlands and Belgium were tested and consequently some more changes were made in the formulation, leading to the final composition. The 500 mg tablets are designed to be broken. Different punch designs were evaluated and the punch design with a scoreline on one side and a breakline on the other side was finalized. Results of the test for subdivision of tablets complied with the Ph. Eur. requirements of the test for subdivision of tablets.

The pharmaceutical development has been sufficiently described.

Manufacturing process

The manufacturing process consists of mixing, granulation, lubrication, compression, coating, and packaging. Validation results of both production sites from two production-scale batches of each tablet strength have been provided, demonstrating that the process is valid and leads to a product that complies with the preset specifications.

Control of excipients

All excipients comply with the latest version of the Ph. Eur., except the Opadry coating, for which an in-house monograph is used. These specifications are acceptable.

Quality control of drug product

The product specifications cover appropriate parameters for this dosage form: appearance, identity, uniformity of mass, dissolution, water, microbial purity, assay and related substances. Validations of the analytical methods have been presented. Batch analysis has been performed on production batches produced at both the developing site and the production sites. The batch analysis results show that the finished products meet the specifications.

Stability of drug product

All presentations have been included in the stability program. The powder has been stored at 25°C/60% RH, 30°C/70% RH, 30°C/65% RH, and 40°C/75% RH. Stability data of the developing site are sufficient to justify the claimed shelf life and storage conditions. Some trends are seen, but they remain within specification. A bulk stability study has been performed on tablets stored in the bulk packaging. No trends were observed during 6 months of storage. For both tablet strengths a shelf life of 36 months without special storage conditions was granted.

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

No material of animal origin is used in the components of the film-coated tablets. The starting material for azithromycin is made by fermentation as starting process, and the only starting material of animal origin, used in small amounts in the process, is bacto-tryptone. This material, produced from a bovine milk derived casein, subsequently hydrolyzed by a protease of porcine origin, is in compliance with the EMEA Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents, as is the alternative skim milk. The milk powder derives from milk, which is sourced from healthy animals fit for human consumption.

II.2 Non clinical aspects

This product is a generic formulation of Azithromax, 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 azithromycin 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

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Azitromycine Mylan 500 mg (Mylan B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Azithromax 500 mg tablets (Pfizer Italiana S.p.A., Italy).

The choice of the reference product

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

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

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 44 (+ 4 alternates) healthy subjects (20 males/24 females), aged 18-47 years. Each subject received a single dose (500 mg) of one of the 2 azithromycin formulations. The tablet was orally administered with 240 ml water after 10 hour fasting period. There were 2 dosing periods, separated by a washout period of at least 4 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, 168, and 216 hours after administration of the products.

Analytical/statistical methods

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

Results

Forty-four subjects were included in the statistical analysis.

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

Treatment N=44	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	4286 \pm 1462	5401 \pm 1970	539 \pm 235	2.0 (1.0-4.0)	54 \pm 40
Reference	4160 \pm 1526	5117 \pm 1785	516 \pm 218	2.5 (0.67-6.0)	44 \pm 21

*Ratio (90% CI)	1.05 (0.95-1.16)	1.07 (0.96-1.18)	1.04 (0.92-1-16)	-	-
CV (%)	28.2	29.4	31.7	-	-
AUC_{0-∞} 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_{max} maximum plasma concentration t_{max} time for maximum concentration t_{1/2} half-life					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{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 azithromycin under fasted conditions, it can be concluded that Azitromycine Mylan 500 mg and Azithromax 500 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Azithromycin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of azithromycin. 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.

Extrapolation to 250 mg tablets

The 250 mg tablet is dose-proportional with the 500 mg tablet. Therefore, no bioequivalence has to be carried out with this formulation, as the results obtained for the 500 mg tablet can be extrapolated to the 250 mg tablet.

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

Azithromycin was first approved in 1991, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of azithromycin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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

During this procedure there was discussion about addition of the contraindication 'severe hepatic impairment' in the SPC. Some member states wanted to include this contraindication (CI), conform the national innovator. But the RMS and some CMSs explicitly did not want to include the CI, although no studies have been conducted regarding the treatment with azithromycin in patients with severe liver disease. They are of the opinion that 'severe hepatic impairment' is not an absolute CI, but a warning as is stated in section 4.4 is appropriate. Furthermore in the approved SPCs of NL/H/1298-1299/DC and NL/H/614/MR, concerning other azithromycin generics, this CI is also not included. On day 90 this issue was still not resolved, and a CMD(h) referral was initiated.

CMD(h) referral

The referral started on 26 November 2009. It was argued that there are insufficient data to justify a contraindication, and that a contraindication should only be included if it is an absolute contraindication (i.e. the product should never be used in that situation).

However, the present product information for the brand leader in the EU is not harmonised and that different decisions have been taken regarding the need for a contraindication for patients with severe hepatic impairment. It was therefore proposed to grant the request and to contraindicate the use of azithromycin in patients with severe hepatic impairment for this product. This was however not agreed upon by all member states.

The contraindication for severe hepatic impairment is based on a previous SPC Guideline in which the lack of data would allow as such. During the discussion it became apparent that in January 2009 an MRP was concluded (PT/H/0146/001/MR) for a line extension of the innovator product Zitromax in which use in patients with severe hepatic impairment is only listed as a warning. So also the innovator company does not find a contraindication necessary based on current knowledge. The listing of a contraindication in the 'older' authorisations may only be owing to a back-log in keeping the SPCs up-to-date.

An article 30 referral was considered not appropriate on the topic of a single contraindication. Therefore, it was agreed to only include a warning in section 4.4, and to contact the innovator to see what data currently are available and to further discuss whether a contraindication is deemed necessary according to the current SPC Guideline. The MAH committed to file for a variation procedure to implement the outcome of the discussion with the innovator regarding the need for a contraindication in patients with severe hepatic impairment, if necessary. Therewith the CMD(h) referral was concluded positively on 25 January 2010.

Readability test

No readability test has been performed, but the MAH submitted a bridging report for Azithromycin, powder for oral suspension (100 mg/5 ml and 200 mg/5 ml) from Sandoz with tested package leaflets for Azithromycin film-coated tablets (FI/H/483/II/01) and Cefpodoxime Proxetil 40 mg/5 ml powder for oral suspension (UK/H/851-854). However the applicant makes no comparison at all between the PIL from Sandoz (subject in the bridging report) and their current PIL. Assessment learns that the latest version of the PIL at issue differs too much from the PIL of Sandoz concerning both the contents (completely different wording, organisation within a section e.g. side effects) as well as the lay-out (headings, bulletpoints, font). Therefore this bridging report alone is not acceptable.

The MAH committed not to place the products on the market until either a bridging report or a PIL user test have been provided via a variation application as evidence that the conditions of patient consultation have been met.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Azitromycine Mylan 250 mg and 500 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Azithromax 250 mg and 500 mg film-coated tablets. Azithromax 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 SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other azithromycin containing products.

The Board followed the advice of the assessors. Azitromycine Mylan 250 mg and 500 mg film-coated tablets were authorised in the Netherlands on 26 September 2005.

During the procedure an issue was raised regarding use in patients with severe hepatic impairment. Some member states argued that a contraindication should be included in the SPC, others found that a warning in section 4.4 is sufficient, as a contraindication is not supported by enough data. A CMD(h) referral was therefore initiated. It was agreed upon to keep the warning as included in section 4.4, and not to include a contraindication. The innovator will be asked for further data on use in patients with severe hepatic impairment, as a result of which inclusion of a contraindication will be discussed. The MAH will follow the innovator SPC. The CMD(h) procedure was finalised on 25 January 2010.

The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Azitromycine Mylan 250 mg and 500 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation.

A European harmonised birth date has been allocated (4 April 1991) and subsequently the first data lock point for azithromycin is April 2011. The first PSUR will cover the period from January 2010 to April 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 1 January 2012

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to put the first three production batches of all dosage strengths from the production plants on stability and to test according to the post-approval stability protocol as laid down.

Product information

- The MAH committed that the products will not be placed on the market until either a bridging report or a PIL user test have been provided as evidence that the conditions of patient consultation have been met via a variation application.
- The MAH committed to file for a variation procedure to implement the outcome of the discussion with the innovator regarding the need for a contraindication in patients with severe hepatic impairment, if necessary.

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

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached