CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Azitromycine Actavis 250 mg and 500 mg, film-coated tablets
Actavis Group hf., Iceland

azithromycin (as dihydrate)

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/2400/001-002/MR
Registration number in the Netherlands: RVG 33804 - 33805

23 April 2013

Pharmacotherapeutic group:	antibacterials for systemic use, macrolids
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:	5 July 2006
Concerned Member States:	250 mg: Mutual recognition procedure with BG, CZ, DK, HU, IE, IS, MT, PL, PT, RO, SE, SK and UK. 500 mg: Mutual recognition procedure with BG, CZ, DK, EE, HU, IE, IS, LT, LV, MT, PL, PT, RO, SE, SK and UK.
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) or 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 Actavis 250 mg and 500 mg, film-coated tablets, from Actavis Group hf. The date of authorisation was on 5 July 2006 in the Netherlands.

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

- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Mild to moderately severe community acquired pneumonia
- 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.

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.

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

The marketing authorisation is granted based on article 10(1) or 10(3) of Directive 2001/83/EC, based on the availability of the innovator strength/pharmaceutical form in the member states.

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 Zithromax 500 mg tablets, registered in the United Kingdom. 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. This generic product can be used instead of its 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, 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 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 azithromycin dihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Azithromycin dihydrate is a semi-synthetic product derived from a fermentation product. It is a white or almost white powder, practically insoluble in water and freely soluble in anhydrous ethanol and methylene chloride. It exists in anhydrous, moderately hygroscopic monohydrate form and non-hygroscopic dihydrate form.

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 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 drug substance specification is in line with the Ph.Eur. monograph and the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches.

Stability of drug substance
The active substance is stable for 24 months if 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
The drug product is a film-coated tablet, available as two product strengths:
250 mg: White to off-white oval, 6.7 x 13.5 mm, biconvex film-coated tablets marked “250” on one side and plain on the other side
500 mg: White to off-white oval, 9.7 x 17.9 mm, biconvex film-coated tablets marked “500” on one side and plain on the other side.

The tablets are packed in PVC/Alu or OPA-PVC-Alu/Alu blisters.

The excipients are:
Tablet core: croscarmellose sodium (E468), magnesium stearate (E572), microcrystalline cellulose (E460), silicium dioxide (E551), poloxamer, povidon (E1201), talc and anhydrous lactose.
Tablet coating: Hypromellose (E464), hydroxypropylcellulose, macrogol, titanium dioxide (E171).

The excipients and packaging are usual for this type of dosage form.

The 250 mg and 500 mg tablets are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed regarded the development of the manufacturing process and comparative dissolution studies with the reference products. The initial development was performed using azithromycin monohydrate. This was later replaced by azithromycin dihydrate. This change did not affect the dissolution of the drug product. The choice of the packaging and manufacturing process are justified. A bioequivalence study was performed with the 500 mg product. The batch used in the BE study was manufactured according to the finalized formula and manufacturing process, except for the use of the monohydrate form of the active substance instead of the dihydrate form. The MAH has demonstrated similarity of dissolution in pH 6.0 medium between the batches manufactured with azithromycin dihydrate and the biobatch that was manufactured with azithromycin monohydrate. Comparative dissolution studies have also been performed using the 250 mg and 500 mg innovator products from different EU member states versus the 500 mg test formulation. All profiles are comparable; the 250 mg tablets are slightly faster dissolving than the 500 mg tablets. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process mainly consists of mixing, wet granulation, drying, final blending and compression. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot-scale batches per strength. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur. or in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, uniformity of dosage units, average weight, disintegration, resistance to crushing, loss on drying, assay, related substances, dissolution and microbiological quality. Except for resistance to crushing, loss on drying and assay, the release and shelf-life requirements are identical. The drug product specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two pilot-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two pilot-scale batches per strength stored at 25°C/60% RH (18 months), 30°C/70% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al/PVC blisters and Al/Al blisters. Supportive stability data are provided on one batch of 250 mg and two batches of 500 mg that were manufactured using azithromycin monohydrate. These batches were stored at 25°C/60% RH (36 months), 30°C/70% RH (12 months) and 40°C/75% RH (6 months). The products were stored in PVC/Al blisters. At accelerated and intermediate storage conditions out-of-specification results are observed for disintegration time for the batches packed in PVC/Al blisters. An increase in loss on drying is seen at all storage conditions. Furthermore, an increase of impurities is seen. Except for disintegration, all parameters remain within the specified limits. The proposed shelf-life of 24 months and storage conditions ‘Do not store above 25°C’ and ‘Store in the original packaging to protect from moisture’ (only for PVC/Al blisters) are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for lactose no excipients of animal origin are used. The magnesium stearate used in the manufacture of the drug product is of vegetable origin. Regarding lactose a statement is present from the

supplier that lactose is derived from milk sourced from healthy animals in the same conditions as milk collected for human consumption, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Zithromax 250 mg and 500 mg tablets, which are available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

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 Actavis 500 mg film-coated tablets (Actavis Group hf., Iceland) is compared with the pharmacokinetic profile of the reference product Zithromax 500 mg tablets (Pfizer, UK).

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.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing, except for the use of the monohydrate form of the active substance instead of the dihydrate form. The use of the monohydrate form has been justified based on comparative dissolution data.

Design
A single-dose, randomized, 2-way cross-over bioequivalence study was carried out under fasted conditions in 38 healthy subjects (8 females and 30 males), aged 18 to 55 years. Each subject received a single dose (500 mg) of both the test and reference azithromycin formulations. The tablets were administered in solid form with 240 ml water after an overnight fast of at least 10 hours. Fasting was continued for 4 hours after dosing. For each subject there were 2 dosing periods, separated by a washout period of 4 weeks. Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, and 120 hours after administration of the products.
The design of this single dose, crossover study under fasting conditions to assess bioequivalence is considered adequate for this application.

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
Thirty-eight healthy adult subjects, were included in this study (including 2 alternatives). One subject (no. 3) was not included due to missing blood samples at 48, 72, 96 and 120 hours after administration in Period I. This subject was replaced by another subject. Pharmacokinetic analysis and statistics included the data of 36 subjects.

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

Treatment N=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4910 ± 1964	5542 ± 2324	505 ± 203	2.33 (1.0 – 5.0)	43 ± 10
Reference	5199 ± 1701	5849 ± 2026	506 ± 135	2.67 (1.33 – 5.0)	43 ± 9
***Ratio (90% CI)**	0.92 (0.84 – 1.01)	0.92 (0.85 - 1.01)	0.96 (0.86 - 1.06)	-	-
CV (%)	22.3	22.2	26.2	-	-

$AUC_{0-\infty}$ 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_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ 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 zaitromycin under fasted conditions, it can be concluded that Azitromycine Actavis 500 mg film-coated tablets and the Zithromax 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 dihydrate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of azithromycin dihydrate. 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.

Biowaiver
A biowaiver for the 250 mg strength has been justified based on the following:
According to the CPMP guideline “Note for guidance on the investigation of bioavailability and bioequivalence” (CPMP/EWP/QWP/1401/98), a bioequivalence study investigating only one strength of a product is acceptable if all of the following conditions are fulfilled:

- The pharmaceutical products are manufactured by the same process
- The pharmacokinetics has been shown to be linear over the therapeutic range
- The qualitative composition of the different strengths is the same
- The formulation of the different strengths is dose proportional
- The dissolution profile should be similar under identical conditions for the additional strengths and the strength of the bio-batch.

These conditions are fulfilled for Azitromycine Actavis.

Risk management plan
Azithromycin was first approved in 1997, 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 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 the reference product Zithromax 250 mg and 500 mg tablets marketed by Pfizer. The SPC has been updated in line with the CMD(h)'s recommendations regarding severe hepatic failure, for which the final wording was established by the CMD(h) in October 2010. The MAH committed to submit a variation to align the Product Information with the outcome of PSUR Worksharing procedure FI/H/PSUR/007/002.

Readability test
The MAH submitted a bridging report in which the daughter PIL of the Azitromycine Actavis 250 mg and 500 mg film-coated tablets was bridged with the already tested mother PIL for the Clarithromycin film-coated tablets. A copy of this User Test report is presented in the bridging report. As Clarithromycin tablets belong to the same drug class and are of the same pharmaceutical form, the SPCs and clinical profiles of both products are similar. Formatted versions of both mother and daughter PIL are included in the bridging report. In the bridging report both content and design matching assessments were performed. It was concluded that:

- the design features of both mother and daughter PILs are identical
- there is sufficient similarity between the two PILs to apply the results of the Clarithromycin film-coated tablets PIL User Test to verify the readability of the daughter PIL.
- the results of the User Test provide sufficient evidence that the information in the Azitromycine Actavis 250 mg and 500 mg film-coated tablets PIL will be 'accessible to and understandable by those who read it, so that they can use the medicine safely and appropriately'.

Therefore separate user testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Azitromycine Actavis 250 mg and 500 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic form of Zithromax 250 mg and 500 mg tablets. Zithromax 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 in accordance 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 Actavis 250 mg and 500 mg film-coated tablets were authorised in the Netherlands on 5 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 Azitromycine Actavis 250 mg and 500 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 21 August 2012.

The date for the first renewal will be: 5 July 2017.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- Process validation for full scaled batches will be performed post authorisation.
- The MAH committed to submit a variation to align the Product Information with the outcome of PSUR Worksharing procedure FI/H/PSUR/007/002.

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
$t_{½}$	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