CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Azitromycine ratiopharm 250 mg and 500 mg, film-coated tablets ratiopharm Nederland B.V., the Netherlands

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/2415/001-002/DC
Registration number in the Netherlands: RVG 110859-110860

24 June 2013

Pharmacotherapeutic group:	antibacterials for systemic use, macrolides
ATC code:	J01FA10
Route of administration:	oral
Therapeutic indication:	bacterial infections when caused by micro-organisms sensitive to azithromycin (see next page)
Prescription status:	prescription only
Date of authorisation in NL:	19 June 2013
Concerned Member States:	Decentralised procedure with DE, ES, IE
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 Azitromycine ratiopharm 250 mg and 500 mg, film-coated tablets from ratiopharm Nederland B.V. The date of authorisation was on 19 June 2013 the Netherlands.

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

- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis
- Acute exarcebation 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 a macrolide antibiotic belonging to the azalide group. The action mechanism of azithromycin is based upon the suppression of bacterial protein synthesis, by binding to the 50S subunit and thus inhibiting the translocation of peptides. Generally, the resistance of different bacterial species to macrolides has been reported to occur by three mechanisms associated with target site alteration, antibiotic modification, or altered antibiotic transport (efflux). The efflux in streptococci is conferred by the mef genes and results in a macrolide-restricted resistance (M phenotype). Target modification is controlled by erm encoded methylases.
A complete cross-resistance exists among erythromycin, azithromycin, other macrolides and lincosamides for *Streptococcus pneumoniae*, beta-haemolytic streptococci of group A, *Enterococcus* spp. and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA).

This decentralised cognition procedure concerns a generic application claiming essential similarity with the innovator products Zithromax 250 mg and 500 mg film-coated tablets which have been registered in the Netherlands (NL License RVG 19432-19433) by Pfizer B.V. since 21 May 1997. 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) 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 Zithromax 500 mg tablets, registered in the UK. 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.*). It is a white or almost white powder which is practically insoluble in water, freely soluble in ethanol and in methylene chloride. Azithromycin exists as two hydrated species (solvates) and as an anhydrous form. The most stable form is a 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 applicant refers to the specification of the Ph.Eur. monograph on azithromycin and the additional CEP requirements. Additional tests and limits are included for identification, particle size and microbial purity. All tests and limits comply with the Ph.Eur. requirements, the specification is acceptable. Batch analysis results are provided on two batches. Results showed compliance with the specification.

Stability of drug substance
Sufficient data on the container closure system has been presented. As a re-test period is not included on the CEP, stability data were submitted. Stability data on the active substance has been provided for ten production scaled batches stored at 25°C/60% RH (36-72 months), 30°C/65%RH (24-60 months), 40°C/40°/75%RH/50°C (6 monhts). The batches were stored in the commercial packaging. Stability results (long term) show some changes, but results remain within limits. Similar results are noted at intermediate conditions. A re-test period of 5 years (60 months) can be granted, The proposed storage condition (Do not store above 30°C) is considered to be justified.

** 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
Azitromycine ratiopharm 250 mg is a white, oblong biconvex film-coated tablet 14.5 x 7.5 mm with imprint AI 250 on one side.
Azitromycine ratiopharm 500 mg is a pale blue, oblong, biconvex film-coated tablet 19.0 x 8.0 mm with imprint AI 500 and break line on one side. The tablet can be divided into equal doses.

The tablets are packed in clear, transparent PVC/Aluminium blisters.

The excipients are:
Core – anhydrous calcium hydrogen phosphate, hypromellose, maize starch, pregelatinised starch, microcrystalline cellulose, magnesium stearate, sodium laurilsulfate.
Coating – hypromellose, colour indigotin lake (E 132) (500 mg tablets only), titanium dioxide (E171), polysorbate 80, talc.

The two strengths are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to create a tablet which could be considered bioequivalent to innovator product Zithromax®. Acceptable comparative dissolution profiles were provided
The test and reference products used in the bioequivalence studies are acceptable from a chemical-pharmaceutical point of view and a waiver for the 250 mg product is acceptable. The 500 mg product has a score line. Breakability of the product was tested and the results showed compliance with the specification as per Ph.Eur. method. The choices of the packaging and manufacturing process are justified.

Manufacturing process
The tablets are manufactured by means of milling, blending, granulation, drying, mixing, tabletting and coating. Holding times should be studied. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using a straightforward process and is considered to be a standard process. Process validation data on the product has been presented for three batches for the 250 mg and 500 mg strength.

Control of excipients
The excipients comply with the specifications of the Ph.Eur., except for the colour indigotin lake. An acceptable in-house specification for the colorant is applied.

Quality control of drug product
The product specification includes tests for description, identification, assay, impurities, uniformity of dosage units, dissolution, water, and microbiological quality. Release and end of shelf-life specifications are identical. The limits are acceptable, as they are in line with European requirements. The analytical methods have been adequately described and validated. Batch analytical results on three batches per strengths have been provided, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for four (250 mg) and 11 (500 mg) production-scale batches stored at 25°C/60% RH (36 months), 30°C/60% RH (12-36 months) and 40°C/75% RH (6 months). The batches were stored in PVC/Al blisters packs. The conditions used in the stability studies are acceptable. At all conditions changes in some impurities are noted, however, no specific pattern is noted and results remain well within limits. All other results are stable. The results of a photostability study demonstrate that the tablets in the immediate packaging are not sensitive for light.
Based on the results provided, the claimed shelf-life of 36 months in the PVC/Al blisters pack can be granted. The claimed storage condition (none required) is also 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 Zithromax, which is 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.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Azitromycine ratiopharm 500 mg (ratiopharm Nederland B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Zithromax 500 mg tablets (Pfizer Ltd, 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.
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, crossover bioequivalence study was carried out under fasted conditions in 24 healthy subjects (12 males/12 females), aged 22-52 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 an overnight fast of at least 12 hours. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 2 weeks.

Blood samples were collected pre-dose and at 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 48, and 72 hours after administration of the products.

A single dose, crossover study under fasting conditions to assess bioequivalence is considered adequate.

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
There were no dropouts. Pharmacokinetic analysis and statistics included the data of 24 subjects.

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

Treatment N=24	**AUC_{0-72}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1209 ± 573	1477 ± 681	182 ± 72	2.5 (0.67 – 5.0)	27.3 ± 10.1
Reference	1233 ± 630	1491 ± 724	166 ± 59	2.5 (0.67 – 5.0)	26.5 ± 10.2

***Ratio (90% CI)**	0.98 (0.90-1.09)	--	1.08 (0.99-1.17)	--	--
CV (%)	27	--	33	--	--

$AUC_{0-\infty}$ 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_{0-72} 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 ratiopharm 500 mg and 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 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 results obtained for the 500 mg tablet can be extrapolated to the 250 mg tablet, as:

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

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 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 decentralised procedure is in accordance with that accepted for the reference product.

Readability test
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. The test consisted of two rounds with 10 participants

each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The test was successful, as 90% of all participants were able to find the information. Of these participants, 90% were able to answer the question correctly. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Azitromycine ratiopharm 250 mg and 500 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zithromax 250 mg and 500 mg film-coated 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 consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Azitromycine ratiopharm 250 mg and 500 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 November 2012. Azitromycine ratiopharm 250 mg and 500 mg, film-coated tablets were authorised in the Netherlands on 19 June 2013.

The date for the first renewal will be: 12 March 2015.

There were no post-approval commitments made during the procedure.

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