PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Azitromycine 200 mg/5 ml ratiopharm, powder for oral suspension
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/2455/001/DC
Registration number in the Netherlands: RVG 111454

19 June 2013

Pharmacotherapeutic group: antibacterials for systemic use, macrolids
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: 23 April 2013
Concerned Member States: Decentralised procedure with ES
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 200 mg/5 ml ratiopharm, powder for oral suspension from ratiopharm Nederland B.V. The date of authorisation was on 23 April 2013 in the Netherlands.

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

- Acute bacterial sinusitis
- Acute bacterial otitis media
- Pharyngitis, tonsillitis
- Acute exacerbation of chronic bronchitis
- 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.

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

Azithromycin powder for oral suspension is indicated in children aged 1 year and older (except for sinusitis treatment), adolescents and adults.

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

Azithromycin is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The action mechanism of azithromycin is based upon the suppression of bacterial protein synthesis, by binding to the 50 S 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 procedure concerns a generic application claiming essential similarity with the innovator product Zithromax Trockensaft, 200 mg/5 ml, which has been registered in Germany by Pfizer since 17 September 1992 (original product). In the Netherlands, Zithromax powder for suspension 200 mg/5 ml (NL License RVG 14999) has been registered since 14 January 1994. 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 200 mg/5 ml suspension, 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, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a "general" monograph, which is applicable for all (pseudo-)polymorphic forms of azithromycin. In this case azithromycin dihydrate is used. Azithromycin dihydrate is a white to off-white crystalline, non-hygroscopic powder.

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. Additional requirements for residual solvents, microbial contamination and particle size are included. The specification is considered adequate to guarantee a consistent, sufficient quality. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
Stability data of long-term stability testing and intermediate stability testing of 13 production-scale batches were submitted. No trends are observed. A re-test period of 5 years, when stored below 30°C is accepted.

* 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 200 mg/5 ml ratiopharm is a white to yellowish-white powder. After reconstitution with an indicated volume of water with a dosing syringe each 5 ml of oral suspension contains 200 mg
azithromycin as dihydrate. Each 1 ml of reconstituted oral suspension contains 40 mg azithromycin as dihydrate.

The powder for solution is packed in HDPE bottles with child-resistant PP closures. The following pack sizes are available:

- **Azithromycin 600 mg/15 ml**
  12.555 g of powder for the preparation of 15 ml suspension
  Each bottle includes an overfill of 5 ml to ensure complete dosing.

- **Azithromycin 900 mg/22.5 ml**
  18.8325 g of powder for the preparation of 22.5 ml suspension
  Each bottle includes an overfill of 2.5 ml to ensure complete dosing.

- **Azithromycin 1200 mg/30 ml**
  25.110 g of powder for the preparation of 30 ml suspension
  Each bottle includes an overfill of 5 ml to ensure complete dosing.

- **Azithromycin 1500 mg/37.5 ml**
  31.3875 g of powder for the preparation of 37.5 ml suspension
  Each bottle includes an overfill of 5 ml to ensure complete dosing.

Multi-dose spoon 2.5/5 ml graduated at 3.75 ml.
Oral dosing syringe (5 ml). The syringe is graduated at every 0.5 ml.

The excipients are: colloidal anhydrous silica (E551), sucrose (3.75 g/5 ml), xanthan gum (E415), trisodium phosphate anhydrous, hydroxypropyl cellulose, cherry flavouring trusil, vanilla flavour, banana flavour.

**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. A measuring cup is supplied for the reconstitution of the drug product. A dosing syringe is included to facilitate dosing.

A bioequivalence study was carried out in order to compare the proposed product with Zithromax® powder for suspension. The UK reference product (Pfizer) was used in the bioequivalence study. In addition the MAH has compared the in vitro dissolution characteristics and the impurity profile of the proposed product with the innovator product. No significant differences between the 3 dissolution media are observed. It could be concluded that the bio-batch has comparable dissolution characteristics as the UK reference product used in the bioequivalence study. The batch used in the bioequivalence study has a slightly different composition and manufacturing process as the currently proposed ones. However, it was adequately demonstrated that the batches with the proposed commercial composition showed comparable in vivo dissolution characteristics compared to the biobatch.

The MAH tested the microbial count on the constituted suspension, and confirmed that the Ph.Eur. requirements were met. Since the constituted product is a multi-dose suspension in water, and no antimicrobial preservatives are added, the MAH also provided results on antimicrobial preservative effectiveness according to Ph.Eur. 5.1.3 on two pilot batches after simulated in-use stability conditions for 5 or 10 days; the results meet the requirements.

**Manufacturing process**

The powder is prepared by a wet granulation process and consists of 6 steps. The particle size of the granulate is determined by the screen size used during manufacturing. The batch formula, applicable for a standard commercial batch size, is in accordance with the drug product composition. The manufacturing process has been sufficiently described. The manufacturing process is considered as a standard process. The proposed fill weights implicate an overage of approximately 1 dose per container. No intermediates are produced. The manufacturing process has been adequately validated for a sufficient number of batches.

**Control of excipients**

For all excipients reference is made to the Ph.Eur., except for the flavours and tribasic sodium phosphate, anhydrous. For trisodium phosphate anhydrous reference is made to the National Formulary (NF). In-
house specifications have been set for the three flavours. The specifications for the excipients are acceptable.

Quality control of drug product
The product specifications cover appropriate parameters for this dosage form: appearance (powder and suspension), identity, uniformity of mass, assay, related substances, dissolution, pH, microbial purity, water content, reconstitution time, resuspendability, and sedimentation speed. Validations of the analytical methods have been presented. Batch analysis has been performed on three batches. The batch analysis results show that the finished product meets the proposed specification.

Stability of drug product
Stability data have been provided on 34 batches of the powder stored at 25°C/60%RH, 30°C/65%RH, and 40°C/75%RH for up to 24 months. A photostability study was performed, demonstrating that the powder and suspension are not sensitive to light. Based on the stability data for the powder a shelf life of 24 months below 25ºC was granted. An in-use stability study has been performed on constituted samples. No significant decrease in the assay or increase in impurities was observed. After reconstitution of azithromycin 15 ml and 22.5 ml, the in-use shelf life is 5 days. For azithromycin 30 ml and 37.5 ml this is 10 days. The reconstituted solution should be stored below 25ºC.

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 200 mg/5 ml ratiopharm (ratiopharm Nederland B.V., NL) is compared with the pharmacokinetic profile of the reference product Zithromax 200 mg/5 ml suspension (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 states. The formula and preparation of the bioequivalence batch is slightly different from the formula proposed for marketing. This difference has been adequately justified.
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 34 healthy subjects (15 females and 19 males), aged 19-45 years. Each subject received a single dose (200 mg/5 ml) of one of the 2 azithromycin formulations. The suspensions were orally administered with 240 ml water after an overnight fast of at least 10 hours. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, 72, 120 and 168 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
Two subjects were withdrawn prior to Period II, because they took concomitant medications to counter adverse events. 32 subjects completed the study entirely and were eligible for pharmacokinetic analysis.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=32</th>
<th>AUC_0-t</th>
<th>AUC_0-∞</th>
<th>C_max</th>
<th>t_max</th>
<th>t_1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>1325 ± 283</td>
<td>1449 ± 307</td>
<td>141 ± 44</td>
<td>2.3 ± 0.9</td>
<td>59 ± 7</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>1273 ± 356</td>
<td>1397 ± 390</td>
<td>153 ± 65</td>
<td>2.4 ± 1.0</td>
<td>59 ± 9</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>1.06 (1.01-1.11)</td>
<td>1.05 (1.00-1.10)</td>
<td>0.96 (0.86-1.07)</td>
<td>--</td>
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<tr>
<td>CV (%)</td>
<td></td>
<td>11.5</td>
<td>11.1</td>
<td>25.8</td>
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</tr>
</tbody>
</table>

AUC_0-t: area under the plasma concentration-time curve from time zero to t hours
AUC_0-∞: area under the plasma concentration-time curve from time zero to infinity
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-∞ 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 Azitromycin 200 mg/5 ml ratiopharm and Zithromax 200 mg/5 ml suspension 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.
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 a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. More than 90% of all participants were able to find the information. Of these participants, 90% must be able to answer the question correctly. No revisions to the PL were required. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Azitromycine 200 mg/5 ml ratiopharm, powder for oral suspension has a proven chemical-pharmaceutical quality and is a generic form of Zithromax powder for suspension. 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 200 mg/5 ml ratiopharm, powder for oral suspension with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 February 2013. Azitromycine 200 mg/5 ml ratiopharm, powder for oral suspension was authorised in the Netherlands on 23 April 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
\( t_{1/2} \) 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>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
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