CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Azitromycine Jubilant 250 mg and 500 mg, film-coated tablets
Jubilant Pharmaceuticals N.V., Belgium

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/1917/001-002/DC
Registration number in the Netherlands: RVG 106459-106460

27 December 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 authorisation in NL:	14 December 2010
Concerned Member States:	Decentralised procedure with BE, DE, UK; additionally for the 500 mg strength – ES, SI, SK
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 Jubilant 250 mg and 500 mg, film-coated tablets from Jubilant Pharmaceuticals N.V. The date of authorisation was on 14 December 2010 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.

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

Azithromycin is an azalide, a sub-class of the macrolide 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 decentralised cognition 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.

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 500 mg product is compared with the pharmacokinetic profile of the reference product Zithromax 500 mg tablets, registered in Germany. 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 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 dihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white powder, which is practically insoluble in water and freely soluble in anhydrous ethanol. Azithromycin exhibits extensive isomerism.

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 drug substance specification is in line with the Ph.Eur. with additional requirements for two impurities and the particle size. The control tests and specifications for drug substance product are adequately drawn up. Batch analytical data have been provided on 2 production-scale batches, demonstrating compliance with the specification.

Stability of drug substance
Stability data have been provided on three full-scale batches stored at 25°C/50% RH for 36 months. No trends or out of specification results were observed, and therefore the proposed re-test period of 48 months was 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 Jubilant 250 mg is a white to off-white, capsule shaped, film-coated tablet debossed with 'AZ' and '250' on one side and plain on other side of the tablet.

Azitromycine Jubilant 500 mg is a white to off-white, capsule shaped, film-coated tablet, debossed with 'AZ' and '500' on either side of score line on one side and plain on other side of the tablet.
The tablet can be divided into equal halves.

The film-coated tablets are packed in white opaque, PVC/PVdC-Al blisters.

The excipients are:
Tablet core – anhydrous calcium hydrogen phosphate**,** hypromellose (E464), croscarmellose sodium, magnesium stearate (E572), pregelatinised starch, sodium lauril sulphate
Tablet coat – hypromellose (E464), lactose monohydrate, titanium dioxide (E171), triacetin.

The two tablet strengths are dose proportional.

Pharmaceutical development
The development of the product has been adequately described, the choice of the excipients is justified and their functions explained. The MAH's objective was to obtain a formulation of azithromycin in two doses of immediate release film-coated tablets: 250 mg and 500 mg. Dissolution profiles have been obtained for the biobatches of test and reference product, and were demonstrated to be similar. The dissolution profiles of the 250 and 500 mg tablet were also shown to be comparable. The MAH performed the test on subdivision of tablets in line with the Ph.Eur. and demonstrated that the 500 mg tablets can be divided in equal parts. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of wet granulation, drying, compression and film-coating. The product is manufactured using conventional manufacturing techniques. Process validation has been performed on three pilot-scale batches per strength. It has been demonstrated that the manufacturing process can adequately produce a product that is in line with the specifications.

Control of excipients
Except for Opadry white all excipients comply with the Ph.Eur. and some additional tests. Opadry white is a well known product. An acceptable in-house specification has been provided. The excipients and their specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, loss on drying, disintegration, uniformity of dosage units by mass variation, dissolution, related substances, assay and microbial limits. The release and shelf-life specifications are identical, with the exception of loss on drying and related substances.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Two batches per strength have been included in the stability study. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in white opaque PVC/PVdC-Aluminium blisters. Twelve months long-term and six months accelerated data are available.
One batch per strength was packed in bulk packaging. Six months long term and accelerated data are available.
The studied parameters remained within the specified limits and there appeared to be no significant change with time. A shelf-life of 24 months was therefore granted for the product packed in PVC/PVdC-Aluminium blisters without special storage conditions.

Two commitments have been made with regard to the finished product; these can be found on page 8 of this report.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Magnesium stearate and lactose monohydrate are derived from animal origin. Magnesium stearate is sourced from bovine derived tallow acid. Written assurance has been provided that all conditions for deactivation of BSE are met.
For lactose a statement has been provided, confirming that the material is derived from healthy animals and obtained under the same conditions as milk for human consumption (conformity to Directive 92/46/EEC).

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 Jubilant 500 mg (Jubilant Pharmaceuticals, Belgium) is compared with the pharmacokinetic profile of the reference product Zithromax 500 mg tablets (Pfizer Pharma GmbH, Germany).

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, balanced, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 62 healthy male subjects, aged 19-38 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 10 hours. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 22 days.

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, 4.5, 5, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 192 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
Five subjects were withdrawn because of adverse events, 1 subject because he did not report at the study centre for 3 consecutive samples, and another subject because he tested positive for drug abuse. Fifty-five subjects completed the study entirely and were included in the pharmacokinetic analysis.

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

Treatment N=55	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	6631 ± 1877	7260 ± 2350	633 ± 211	2.5 ± 1.0	67 ± 27
Reference	6432 ± 2190	6959 ± 2485	626 ± 192	2.1 ± 0.9	62 ± 17

***Ratio (90% CI)**	1.06 (0.98-1.14)	1.06 (0.99-1.15)	1.02 (0.93-1.12)	--	--
CV (%)	23.4	24.0	30.8	--	--

$AUC_{0-\infty}$ 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 azithromycin under fasted conditions, it can be concluded that Azitromycine Jubilant 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 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 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 SPC is consistent with that of the reference product and other azithromycin generics. However, during the procedure concerns were raised regarding the SPC. The following warning had been removed from section 4.1, and one of the CMS requested addition to section 4.4: 'Azithromycin is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more (see section 5.1)'.
In addition this CMS requested that several warnings were placed back in section 4.4 after these had been removed following earlier comments from another member state.

In order to solve these issues the RMS proposed to replace the disputed warnings in section 4.1 with one general warning in section 4.4 regarding high levels of resistance across the EU measured in species that are relevant to the indications claimed for azithromycin:

The selection of azithromycin to treat an individual patient should take into account the appropriateness of using a macrolide antibacterial agent based on adequate diagnosis to ascertain the bacterial etiology of the infection in the approved indications and the prevalence of resistance to azithromycin or other macrolides.
In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics.
As for other macrolides, high resistance rates of Streptococcus pneumoniae have been reported for azithromycin in some European countries (see section 5.1). This should be taken into account when treating infections caused by Streptococcus pneumoniae.
In bacterial pharyngitis the use of azithromycin is recommended only in cases where first line therapy with beta-lactams is not possible.

This solution was agreed upon by all member states.

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 2 participants, followed by two rounds with 10 participants each. Fifteen questions covered the content of the PIL and 4 questions were asked to obtain participants' opinion on style and lay-out of the PIL. The results were presented in a clear way. The pre-determined limits were easily met: readability may be considered established. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Azitromycine Jubilant 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.

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 Jubilant 250 mg and 500 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 October 2010. Azitromycine Jubilant 250 mg and 500 mg, film-coated tablets were authorised in the Netherlands on 14 December 2010.

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 October 2010 to April 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 December 2014.

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

Quality - medicinal product

- The MAH committed to validate the first three consecutive batches of Azithromycin 250 mg and 500 mg film-coated tablets.
- The MAH committed to perform a stability study on the first three production batches of Azithromycin 250 mg and 500 mg film-coated tablets in marketed container/closure system. The first three production batches will be placed on a long-term stability study for the duration of the proposed shelf life and on accelerated condition for a period of six months.

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