Public Assessment Report

Scientific discussion

Zigilex ODT
20 mg and 100 mg orodispersible tablets

(Azithromycin)

DK/H/2437/001-002/DC

2 March 2016

This module reflects the scientific discussion for the approval of Zigilex ODT. The procedure was finalised on 22 July 2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Zigilex ODT 20 mg and 100 mg orodispersible tablets, from PharmaSwiss Ceska republika s.r.o.

The product is indicated for the following infections if caused by bacteria susceptible:
- Upper respiratory tract infections: sinusitis, pharyngitis, tonsillitis
- Lower respiratory tract infections: bronchitis, mild to moderately severe community-acquired pneumonia
- Acute otitis media
- Mild to moderately severe skin and soft tissue infections, e.g. folliculitis, cellulitis, erysipelas
- Uncomplicated urethritis and cervicitis caused by *Chlamydia trachomatis.*

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

Azithromycin is an azalide, a sub-class of the macrolide antibiotics. It suppresses bacterial protein synthesis, by binding to the 50 S subunit and thus inhibiting the RNA-dependent protein-synthesis.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Sumamed 20 mg/ml powder for syrup, which has been registered in Slovak Republic by Teva Pharmaceuticals Slovakia s.r.o since 2004.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Each 20 mg orodispersible tablet contains 20 mg azithromycin as azithromycin dihydrate. The tablet is white or almost white to cream, of slightly marbled surface, round of 8 mm diameter, on one side convex, on the other side concave, with concave break-mark on concave side tablet. The tablet can be divided into equal doses.

Each 100 mg orodispersible tablet contains 100 mg azithromycin as azithromycin dihydrate. The tablets is white or almost white to cream of slightly marbled surface, oblong of 18.9 mm length, biconvex tablet.

The tablets are packed in PVC/PE/PVDC/Aluminium blisters in pack sizes of:
20 mg: 9, 12 and 15 orodispersible tablets.
100 mg: 3 and 6 orodispersible tablets.
However, not all pack sizes may be marketed.

The orodispersible tablets contain: Cellulose microcrystalline type 101; Silica, colloidal anhydrous (E551); Basic butylated methacrylate copolymer; Sodium laurilsulfate; Dibutyl sebacate; Talc; Titanium dioxide (E171); Cellulose microcrystalline type 200; Hydroxypropylcellulose low substituted; Apple flavour [containing as main components maltodextrin, arabic gum (E414), triacetin (E1518), natural flavouring substances]; Sucralose (E955) and Magnesium stearate.

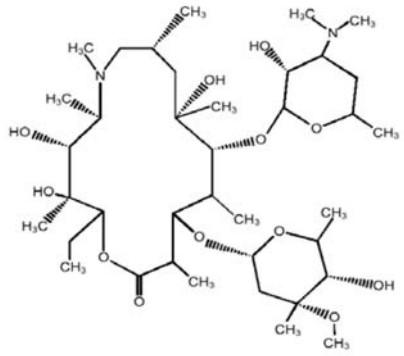
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The active substance, azithromycin dihydrate, is described in the European Pharmacopoeia. It is a white or almost white powder. It is practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride.

INN: Azithromycin dihydrate
Chemical name: (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*methyl-α-L-*ribo*hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-rideoxy-3-(dimethylamino)-β-D*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one, x-hydrate (x =2).

Empirical formula: $C_{38}H_{72}N_2O_{12}$, x H_2O, x = 2
Molecular mass: 749 (anhydrous substance)
Structural formula:



For the supplier of the active substance, a CEP is provided.

The drug substance specification from the drug product manufacturer is presented. Batch analysis data demonstrate the conformity with the Ph. Eur. monograph.

The re-test period and storage conditions are according to the CEP.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The pharmaceutical development is considered sufficient.

Both strengths are manufactured from the same granulate. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three batches of each strength. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The medicinal product is not sensitive to light.

A shelf-life of 48 months when stored in the original packaging in order to protect from moisture was accepted.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of azithromycin are well known. As azithromycin is a widely used, well-known active substance, the MAH has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview report refers 65 publications up to year 2014. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since azithromycin is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Azithromycin is a well-known active substance with established efficacy and tolerability. As azithromycin is a widely used, well-known active substance, the MAH has not provided additional studies (apart from a supportive bioequivalence study referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical report refers 151 publications up to year 2014. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

To support the application the MAH submitted as report one bioequivalence study conducted on the highest strenght of 100 mg in line with BE guidance. Zigilex 100 mg orodispersible tablets was compared to Sumamed 100 mg/5 ml granules for oral suspension, Teva Pharmaceuticals Polska Sp. z o.o., from the Polish market.

Biowaiver
The MAH applied for a strenght biowaiver of Zigilex ODT 20 mg orodispersible tablets. The biowaiver of the 20 mg was accepted since the general biowaiver criteria were fulfilled.

Bioequivalence study
The study was was an open-label, randomised, three-treatment, three-sequence, three-period, three-way crossover, single-dose bioavailablity study conducted under fasting conditions with a wash-out period of 21 days between each of the three periods. 100 mg was administered in each period.

A total of 40 healthy male/female subjects participated in the study. 39 subjected completed the study. 37 subjects (test product without water), 38 subjects (test product with water) and 39 subjects (reference products) were included in the statistical and pharmacokinetic analysis.

The primary variables AUC_{0-72} and C_{max} were evaluated for bioequivalence.

The ratios of the geometric least square means of the test product to reference product for log-transformed AUC_{0-72} and C_{max} of azithromycin should be within the 80.00-125.00% range of the 90% confidence interval in order for bioequivalence to be concluded.

Results

Table 1. Descriptive statistics of pharmacokinetic parameters for azithromycin

Pharmacokinetic parameter [Unit] Azithomycin	Test Macromax without water (T) N = 37	Test Macromax with water (Tw) N = 38	Reference Sumamed® (R) N = 39
C_{max} [ng/mL]			
Mean (SD)	58,36 (27,29)	70,81 (35,47)	67,97 (29,33)
Geo. Mean	51,07	63,85	62,04
Median	59,76	62,94	63,04
Minimum - Maximum	6,72 – 124,26	18,80 – 198,58	21,89 – 144,36
AUC_{0-72h} [ng · h/mL]			
Mean (SD)	479,29 (26,58)	529,38 (140,71)	538,08 (147,26)
Geo. Mean	426,48	510,37	516,95
Median	453,76	533,21	519,77
Minimum - Maximum	65,02 – 987,57	274,44 – 805,30	275,94 – 802,41
t_{max} [h]			
Mean (SD)	3,49 (1,02)	3,53 (1,03)	3,10 (0,90)
Geo. Mean	3,34	3,38	2,98
Median	3,50	3,25	3,00
Minimum - Maximum	1,50 – 5,00	1,50 – 5,00	1,50 – 5,00
$t_{1/2}$ [h]			
Mean (SD)	36,71 (7,11)	34,69 (6.47)	36,44 (8,27)
Geo. Mean	36,05	34,18	35,64
Median	36,63	33,71	35,30
Minimum - Maximum	25,06 – 51,94	26,05 – 59,25	26,03 – 66,10

*Statistical evaluation was performed on the set of n = 38 subjects for treatment Tw, n=37 subjects for treatment T and n=39 for treatment R.

Table 2. Point estimates and 90% confidence intervals for (log-transformed) azithromycin pharmacokinetic parameters

Pharmacokinetic parameter [unit] azithromycin	Point estimate Tw/R ratio [%]	Point estimate T/R ratio [%]
C_{max} [ng/mL]	102.92	82,31
90% CI [%	88,96 – 119,07	70,34 – 96,33
AUC_{0-72h} [ng*h/mL]	98.73	82,50
90% CI [%	91,42 – 106,61	73,73 – 92,31
$t_{1/2}$ [h]	95.90	101,13
90% CI [%	89,97 – 102,23	95,11 – 107,53

*Statistical evaluation was performed on the set of n=38 subjects for treatment T_W/R ratio n=37 subjects for treatment T/R ratio

The 90% confidence intervals for the ratio between test and reference were within the acceptance criteria 80.00-125.00 % for AUC_{0-72} and C_{max} for the test product Zigilex ODT and the reference product Sumamed.

Pharmacokinetic conclusion
Based on the submitted bioequivalence study, Zigilex ODT 100 mg orodispersible tablets is considered bioequivalent with the reference product Sumamed 100 mg/5 ml granules for oral suspension, Teva Pharmaceuticals Polska Sp. z o.o.

The justification for waiving study on the lower strength (20 mg), based on the study with the 100 mg strength, was accepted and the results for the study on the 100 mg strength can be extrapolated to the lower strength.

The RMS 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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Zigilex ODT.

The following summary list of safety concerns with no additional pharmacovigilance measures or risk minimisation measures has been agreed:

Table 3. Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• Anaphylaxis • Severe cutaneous adverse reactions (SCARs) • Hepatic toxicity including hepatic failure • Hearing impairment including deafness and/or tinnitus • QT prolongation and Torsade de pointes • Drug-drug interactions with P-gp substrates, cyclosporin, active substances known to prolong QT interval and lovastatin • Leucopenia, neutropenia
Important potential risks	• Drug-drug interactions with ergot derivatives, theophylline and coumarin type oral anticoagulants
Missing information	• Safety and efficacy for the prevention or treatment of MAC (Mycobacterium Avium Complex) in children • Use in patients with renal and hepatic impairment • Use in pregnancy and lactation

V. USER CONSULTATION

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 language used for the purpose of user testing the PIL was Polish.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The test consisted of a pilot test with 6 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Zigilex ODT 20 mg and 100 mg orodispersible tablets has a proven chemical-pharmaceutical quality and is a generic form of Sumamed. Sumamed 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.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity was demonstrated for Zigilex ODT with the reference product, and therefore granted a marketing authorisation. The decentralised procedure was finalised on 22 July 2015. Zigilex ODT was authorised in Denmark on 10 December 2015.

PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. According to the EURD list, no routine PSURs need to be submitted.

The date for the first renewal will be: 22 July 2020.

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