

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Bazyt 15 mg/g, eye drops, solution
Laboratoires THEA, France

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/2356/001/DC
Registration number in the Netherlands: RVG 109580

4 March 2013

Pharmacotherapeutic group:	antibiotics
ATC code:	S01AA26
Route of administration:	ocular
Therapeutic indication:	local antibacterial treatment of conjunctivitis
Prescription status:	prescription only
Date of authorisation in NL:	19 February 2013
Concerned Member States:	Decentralised procedure with DE
Application type/legal basis:	Directive 2001/83/EC, Article 8(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 Bazyt 15 mg/g, eye drops, solution from Laboratoires THEA. The date of authorisation was on 19 February 2013 in the Netherlands.

The product is indicated for local antibacterial treatment of conjunctivitis caused by susceptible strains:

- Purulent bacterial conjunctivitis,
- Trachomatous conjunctivitis caused by *Chlamydia trachomatis*.

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 second-generation macrolide antibiotic belonging to the azalide group. It inhibits the synthesis of bacterial proteins by binding to the 50S ribosomal subunit and preventing peptide translocation.

This decentralised procedure concerns a full application based on article 8(3) of Council Directive 2001/83/EC. The application concerns a copy dossier of AZYTER (NL License RVG 34031), registered in the Netherlands since February 2008, after finalisation of an MRP. Recently, a Repeat Use Procedure for AZYTER has been finalized (NL/H/855/001/E/001) in which Germany was also included as CMS.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC (full dossier for a product containing a known active substance).

This 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.

The authorisation for this copy dossier is therefore linked to the 'original' authorised medicinal product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this copy dossier.

Scientific advice was given by the Agence Française de Sécurité Sanitaire de Produits de Santé (AFSSAPS) on 29 January 2003, 20 October 2003 and 8 January 2004.

No paediatric development programme has been submitted. Use in paediatric populations has been justified.

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 white or almost white powder, which is practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride.

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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEP. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance

The active substance is stable for 36 months when 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

Bazyt 15 mg/g is a clear, colourless to slightly yellow, oily solution. Each gram of solution contains 15 mg of azithromycin dihydrate equivalent to 14.3 mg of azithromycin.

The product is packed in single-dose low-density polyethylene containers. One single-dose container of 250 mg solution contains 3.75 milligrams of azithromycin dihydrate.

The only excipients is: triglycerides, medium-chain.

Pharmaceutical development

No topical ophthalmic formulation of azithromycin was available before the registration of AZYTER (NL/H/855). Bazyt 15 mg/g is a copy dossier of AZYTER. The aim of the formulation development was to propose the first macrolide in a formulation for ocular use, easy to use, allowing a short duration of treatment for the targeted indications and presenting an alternative to the oral "off-labelled" use for trachoma. An adequate description of the pharmaceutical development has been provided for the eye drop product at issue, including all aspects of the chosen oily excipient, *triglycerides, medium-chain*, sterilization aspects (sterilizing filtration), physical and microbiological aspects of the chosen single-dose

container, stability aspects including sensitivity to oxygen, and manufacturing process development aspects.

Manufacturing process

There are two manufacturing sites for the finished product. The manufacturing process starts by the preparation of the solution. The bulk solution is then sterilised by filtration and immediately filled in-line with the formation of the single-dose units. No overage is applied. Validation data shows that the manufacturing process has been adequately validated from microbiological and physico-chemical point of view. No impact of light was observed.

Control of excipients

Triglycerides, medium-chain meets the requirements of Ph. Eur. monograph on Triglycerides, medium-chain, and nitrogen is in accordance with the Ph. Eur. monograph. These specifications are acceptable.

Quality control of drug product

Adequate specifications have been provided on appearance, colour, viscosity, water content, extractable weight, identification, assay, impurities and sterility. The clear oily liquid should be practically free from foreign particles. Previous studies in a refrigerator (2-8°C) and freezer (-27°C) demonstrated that storage in a freezer or refrigerator has no influence on the appearance, opalescence and number of particles. Therefore, it is not necessary to add an additional storage recommendation like "Do not refrigerate or freeze".

All analytical methods have been described and validated.

From one manufacture, batch analysis results of 1 pilot-scale batch and 6 full-scale batches were provided. From the other manufacturer, batch analysis results of 3 full-scale batches were presented, all in transparent single-dose units. All certificates of analysis still possess previous specifications, however, based on the results for each known impurity, each unknown impurity and total impurities it is concluded that the currently proposed release specifications are easily met.

Container closure system

Single-dose containers of polyethylene are used. The LDPE material from both single-use units complies with Ph. Eur. 3.1.4 Polyethylene without additives for containers for preparations for parenteral use and for ophthalmic preparations. The LDPE is also in accordance with Directive 2002/72/EC. The shape and dimensions of both single-dose units as applied by both manufacturers are not identical. According to the SPC the dosage of the eye drop product is expressed by the number of drops. Previously a study has been performed regarding the drop size using 6 batches from one manufacturer and 2 batches from the second manufacturer. It has been made assumable that the order of magnitude of the drop size resulting from both types of containers is comparable. The dosage is one drop per eye, two times per day, *i.e.* two drops for two eyes if both eyes are affected. The provided drop size indication (22 mg ± 5 mg (17 to 27 mg) is considered as being sufficiently accurate for the intended eye drop treatment.

Stability of drug product

A shelf life of 18 months for the product before opening of the single-dose container if stored not above 25°C is claimed. The initial three batches as used in the process validation study from the first manufacturer have been put on stability. Hereafter another 5 batches have been put on stability. Also 3 full-scale batches from the other supplier have been put on stability. Photostability testing concluded that the drug substance is light-sensitive. The proposed shelf-life specification on impurities is adequate based on the stability batches. Based on all provided data the granted shelf-life is 18 months if stored in the two types of single-dose polyethylene containers not above 25°C. Additional storage label: Keep the single-dose containers in the sachet in order to protect them from light.

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

Azithromycin is a second generation macrolide antibiotic. It is structurally related to the macrolide erythromycin. Azithromycin's mechanism of action is similar to other macrolide agents: It binds to the 50S ribosomal subunit of susceptible organisms and inhibits mRNA-directed protein synthesis. From preclinical point of view, Bazyt 15 mg/g, eye drops, solution can be registered, since the product is identical to AZYTER.

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

Pharmacokinetics

To support the pharmacokinetics of this application, five studies were submitted evaluating azithromycin tear levels (study LT1225-PI2-03/02), azithromycin concentrations in conjunctiva after repeated instillation (study LT1225-P14-11/02), and ocular azithromycin pharmacokinetics (study LT1225-PI1-09/01(Fr), LT1225-PI1-09/01(AS) and LT1225-P13-07/02). Overall, a high variability is observed in the azithromycin tear and conjunctiva concentrations, and therefore the obtained results should be interpreted with care. Notwithstanding, the results indicate dose dependent concentrations, with a higher exposure for the 1.5% compared to the 1% dose. Higher concentrations were observed at day 3 compared to day 1 in case twice daily instillation of one eye drop was applied. Plasma samples obtained at day 3 were below the LOD of 0.2 ng/ml. Comparison with oral azithromycin, subjects receiving one drop of 1.5% tear drops twice daily for three days (the recommended dose in the SPC) showed higher tear and conjunctiva azithromycin concentrations compared to those observed after orally dosed azithromycin (1 g at day 1) although the variability in azithromycin tear and conjunctiva concentrations after oral azithromycin administration is considerably lower compared to that after instillation in the eye.

Pharmacodynamics

The results of the pharmacokinetic studies suggested that T1225 1.5% eye drops administered BID for 3 days had the best PK/PD profile. It can achieve the required conjunctival AZM concentrations, 8 days after initiation of the treatment with T1225 (*i.e.* 5 days after the last instillation of the proposed dosing regimen), whereas 1 day of treatment did not appear to be sufficient.

The choice of the 1.5% azithromycin concentration in AZYTER/Bazyt eye drops can be endorsed as evidenced by the data and when subjected to the clinical trial results.

Clinical efficacy

Active trachoma

The study design, endpoints, duration, and statistical procedures were appropriate. The results are in support of the T1225 1.5% 3 days therapy and the comparability of the results with the reference therapy in paediatric patients with uncomplicated trachoma in endemic areas in the developing world. The absence of placebo control is ethically well justified in the light of the seriousness of this eye infection. The somewhat lower performance of the 2 days regimen in this study and less favourable pharmacokinetic/pharmacodynamic profile of the latter regimen and the lower concentrations are supportive of the internal validity of the study results.

The choice of the comparator, however, is primarily based on reported efficacy of Zithromax oral treatment in trachoma in the publications and the recommendation of the WHO. It is unfortunate that this innovator product is not registered in EU countries including the Netherlands or in the USA for the sought indication. The applicant has provided an extensive review of the bibliographical evidence for the efficacy of antibiotics and in particular azithromycin in the management of trachoma. Not choosing the treatment with 1% tetracycline ointment is well argued by the applicant. The clinical cure rates observed in the present study were relatively high. This was due to the low proportion of microbiologically-positive patients, and the efforts made to avoid re-infection including treatment of contact persons with azithromycin and an information campaign regarding environmental risk factors.

Overall, the available published data and present results of oral AZM are reconcilable and support the external validity of present study results in acute uncomplicated trachoma.

Table CO1 – Cure at the End of the Study in the Worse Eye (PP Set)

Cure rate		Exact 95% CI on Cure Rate	Difference in Cure Rate	Exact 95% CI on Difference	Non-inferiority of T1225 versus oral AZM
Treatment Group					
T1225 2 days (N = 199)	93.0%	[88.5%;96.1%]			
T1225 3 days (N = 190)	96.3%	[92.6%;98.5%]			
oral AZM (N = 179)	96.6%	[92.9%;98.8%]			
Comparisons between groups					
T1225 3 days minus oral AZM			-0.3%	[-4.6%;3.9%]	Accepted
T1225 2 days minus oral AZM			-3.7%	[-8.6%;1.0%]	Accepted

Purulent Bacterial Conjunctivitis

The study design, endpoints, duration, and statistical procedures were appropriate. The PP analysis of the clinical results in patients with positive bacteriological cultures at baseline support the non-inferiority of the efficacy of T1225 1.5% 3 days (6 drops per eye) treatment of purulent conjunctivitis to that of the reference therapy with tobramycin (up to 8 times daily for 2 days, then QID for 5 days) in children and adult patients. Approximately 150 (52 for PP population) of the included patients were younger than 18 years, including 2-3 newborns per group. This is also supported by the bacteriological outcome results.

The absence of placebo control is ethically well justified as only truly purulent bacterial conjunctivitis was included. These cases were moderate to severe in about 75% of the patients as shown by the severity distribution of the cardinal signs (bulbar conjunctival injection and conjunctival purulent discharge). From the bacteriological point of view, however, it should be remarked that not all isolates in particular *S. epidermidis* need to be the causative agents as they could belong to the normal non-pathogenic flora; in addition the high activity in the limited cases of *enterobacteriaceae* isolates whereas these are inherently resistant to azithromycin could be explained by other factors than the activity of azithromycin. The potential high placebo effect (as documented in the literature) could have contributed to the observed high cure rates in this indication. Nevertheless, the internal validity of the study results in the tested patient population with moderate to severe infection in ¾ of the cases is supported by the detection of differences as a country effect and a significantly higher clinical cure rate with T1225 on day 3. The results are consistent with results with topical tobramycin and other antibiotics (including fluoroquinolones) from literature.

Table CO2 – Purulent conjunctivitis– Clinical Cure in the Worse Eye on Day 9

Set	Number (%) of patients with clinical cure in the worse eye on day 9		Non-inferiority analysis (T1225 minus tobramycin)		
	T1225 ^a	Tobramycin ^a	Difference in cure rate	Exact 2 sided 95% CI on difference	Non-inferiority
PP	215 (87.8)	202 (89.4)	-1.6%	[-7.5%;4.4%]	Accepted
MITT	231 (85.6)	216 (86.1)	-0.5%	[-6.6%;5.8%]	Accepted
ITT	447 (85.3)	440 (84.8)	0.5%	[-3.8%;4.9%]	Accepted

Clinical safety

Overall, local and systemic safety clinical trial data of T1225 1.5% eye drops can be considered sufficient. T1225 1.5% eye drops were safe for the ocular surface with the recommended dosing regimen in patients and may induce some symptoms upon instillation. Clinically relevant itching/burning/stinging was notably higher upon instillation of T1225 compared with tobramycin but remained $\leq 10\%$ level. These appeared to be associated with the vehicle of T1225 and to a similar extent as observed in the vehicle controlled phase I studies. The incidence of clinically relevant stickiness, foreign body sensation, blurred vision and tearing was low.

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.

PSUR submission

Azithromycin-containing products participate in the PSUR Worksharing Project (Harmonised Birthdate 4 Apr 1991, FI/H/PSUR/0007/002). However, until now, no PSUR data for ophthalmic preparations of azithromycin have been assessed in a worksharing procedure. For AZYTER, the following PSUR schedule was applicable:

o Before initial placing on the EU market:

- 6-monthly PSUR submissions after the end of the procedure.

o After initial placing on the EU market:

- 6-monthly PSUR submissions will be continued until two full years of marketing experience on the EU market;
- Then, yearly PSURs for the following two years;
- Thereafter PSURs will be submitted at 3-yearly intervals.

The MAH committed to submit the PSUR data according to the PSUR schedule as agreed on for AZYTER. The next PSUR concerning AZYTER will cover the period from 31 January 2011 to 30 January 2012. After this PSUR, the next PSUR will be submitted according to the Data Lock Point concerning the active ingredient azithromycin published in the PSUR Worksharing List: April 2014. This means that the next PSUR for Bazyt, eye drops, solution will cover the period from 31 January 2012 to 31 April 2014.

Product information

SPC

The product information has been brought in line with the product information of AZYTER (NL/H/855/001).

Readability test

For the registration of AZYTER a user test was provided and approved. Furthermore the MAH made a comparison between the PL during the user test and the Proposed PL for Bazyt. Therefore the Bazyt package leaflet is fully in compliance with the requirements of Directive 2001/83/EC as amended by Directive 2004/27/EC and of the Readability Guideline.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Bazyt 15 mg/g, eye drops, solution has a proven chemical-pharmaceutical quality and is identical to AZYTER eye drops. AZYTER is a well-known medicinal product with an established favourable efficacy and safety profile.

Clinical efficacy and safety in active trachoma and purulent bacterial conjunctivitis has been demonstrated.

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 AZYTER. 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 acceptable efficacy and safety has been demonstrated for Bazyt 15 mg/g, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 22 February 2012. Bazyt 15 mg/g, eye drops, solution was authorised in the Netherlands on 19 February 2013.

The date for the first renewal will be: 30 December 2014.

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

Quality - active substance

- The MAH committed to submit a type IA variation to update the active ingredient specifications according to the last version of the Ph.Eur. monograph.

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

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached