Public Assessment Report for paediatric studies submitted in accordance with Article 45 - 46 of Regulation (EC) No1901/2006, as amended

AZITHROMYCIN

Part II

AZYTER 15mg/g, eye drops, solution in single-dose container

HU/W/0002/pdWS/001

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<th>Rapporteur:</th>
<th>Hungary</th>
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<td>Finalisation procedure (day 120):</td>
<td>17.07.2012</td>
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<td>Date of finalisation of PAR</td>
<td>30.08.2012</td>
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I. EXECUTIVE SUMMARY

Azithromycin is a macrolid antibacterial agent which has been in clinical use in Europe since 1991. Azithromycin is the prototype azalide antibiotic. It differs from erythromycin by insertion of a methyl-substituted nitrogen at position 9A in the lactone ring, creating a 15-membered structure. This modification confers unique pharmacokinetic properties, resulting in high tissue concentration and increased tissue retention. The microbiological spectrum of activity of azithromycin is similar to that of erythromycin, but with enhanced potency against *Mycobacterium avium* complex (MAC) and gram-negative organisms, particularly *Haemophilus influenzae*.

Azithromycin is available as:

- **immediate release formulations**
  - capsules, tablets, powder for oral suspension and sachets- available for children in EU countries (see Part I, section VII)
  - intravenous solution - the safety and efficacy in children has not been established
- **prolonged release formulation**
  - for oral suspension - not currently approved for use in paediatric patients in Europe
- **topical formulation**
  - eye drops - available for children in 9 EU countries (see Part II, section VII).

Worldwide, as of January 2011, azithromycin has received marketing authorization in 128 countries and is marketed in 125 countries in at least 1 formulation.

Two MAHs submitted studies. The oral immediate release formulations and the ophthalmic preparation assessed separately as Part I and Part II accordingly. This assessment covers the paediatric use of the ophthalmic preparation.

In the approved SmPC the indications are common for adults and children and there is a posology for azithromycin eye drops in children.

One MAH submitted three Phase III completed paediatric studies for Azithromycin dihydrate, in accordance with Article 45 - 46 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use. Two studies were completed before January 2008 and one was conducted and completed in 2008.

No SmPC changes are proposed by the MAH.
II. RECOMMENDATION

The ongoing variation procedure (NL/H0855/01/II/10) resolves the issues. No further action required.

III. INTRODUCTION

One MAH submitted three Phase III completed paediatric studies for Azithromycin dihydrate, in accordance with Article 45 - 46 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies don’t influence the benefit risk for Azyter 15mg/g, eye drops, solution in single-dose container (Azyter) and that there is no consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- A cover letter including SmPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product
- Reference to PSURs already submitted
- LT1225-PIII-06/06 study report.

The registration of Azyter was performed as a decentralised procedure in EU (NL/H/855/01/DC) and ended on 30 July 2007. At the end the following indication and posology were approved:

4.1 Therapeutic indications
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.

4.2 Posology and method of administration

Posology

Adults, Adolescents (12 to 17 years), children (2 to 11 years):
Instil one drop in the conjunctival fornix twice a day, morning and evening, during three days.
It is unnecessary to prolong treatment beyond three days.
Adherence to the dosing regimen is important for the success of treatment.

Children (1 to 2 years)
For trachomatous conjunctivitis, no dose adjustment is necessary.
For purulent bacterial conjunctivitis, there is no sufficient experience with Azyter in children younger than 2 years of age (see section 5.1).

Children (less than 1 year)
There is no sufficient experience with Azyter in children younger than 1 year of age for trachomatous conjunctivitis as well as for purulent bacterial conjunctivitis (see section 5.1).

Elderly patients:
No dose adjustment is necessary.

Method of administration
Ocular use.
The patient should be advised to:
- thoroughly wash hands before and after the instillation,
- avoid touching the eye or eyelids with the dropper tip of the single-dose container,
- discard the single-dose container after use, and not keep it for subsequent use.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

During clinical trials the product was named 1.5% T1225.
Batch numbers: 7, 15 and 20.

IV.2 Non-clinical aspects

No non-clinical studies were submitted.

IV.3 Clinical aspects

1. Introduction

The MAH submitted three clinical study reports for:

<table>
<thead>
<tr>
<th>Study number Country Date</th>
<th>Treatment groups (n) patients</th>
<th>Dosage regimen</th>
<th>Primary objective</th>
<th>Secondary objectives</th>
</tr>
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<tbody>
<tr>
<td>T1225–PIII–10/03 Guinea, Pakistan</td>
<td>1.5% T1225 (223) 1.5% T1225 (225) Zithromax® (221) (oral azithromycin)</td>
<td>1 drop twice daily for 2 days 1 drop twice daily for 3 days 1 oral single dose (20 mg/kg)</td>
<td>Clinical efficacy of T1225 in the treatment of trachoma</td>
<td>Safety of T1225 in patients suffering from trachoma</td>
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<td>T1225–PIII–11/03 France, Portugal, Bulgaria, Romania, Guinea, India, Morocco, Tunisia May 2004 to June 2005</td>
<td>1.5% T1225 (508) Tobrex® (507) (tobramycin 0.3% eye drops)</td>
<td>1 drop twice daily for 3 days 1 drop every 2 hrs while awake (up to 8 times per day) for 2 days then 1 drop 4 times daily for 5 days</td>
<td>Efficacy of T1225 in the treatment of purulent bacterial conjunctivitis</td>
<td>Safety of T1225 in patients suffering from purulent bacterial conjunctivitis</td>
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<tr>
<td>LT1225-PIII-06/06 Algeria</td>
<td>1.5% T1225 (326)</td>
<td>1 drop twice daily for 3 days</td>
<td>Clinical efficacy of T1225 in the treatment of trachoma</td>
<td>Safety of T1225 in patients suffering from trachoma</td>
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In total, 1282 patients received T1225 1.5%, 221 patients received oral azithromycin and 507 0.3% tobramycin eye drops.
2. Clinical studies

Trachoma Indication

Study No. LT1225-PIII-10/03: Clinical Efficacy and Safety of 2 Dosing Regimens of T1225 Eye Drops 1.5% (Instilled Twice Daily for 2 or 3 Days) versus Oral Azithromycin in Treatment of Trachoma

Description

The study was designed and conducted between 30 January 2004 and 16 May 2004, in accordance with globally accepted standards of Good Clinical Practice (GCP), applicable guidelines (in particular CPMP/ICH/2711/99 and CPMP/EWP/462/95 for clinical trials in children, and CPMP/EWP/558/95 for the treatment of bacterial infections), the Declaration of Helsinki (2000) and local regulations.

Investigation centers: Guinea Conacry (West Africa) – 21 villages
Pakistan (South East Asia) – 6 villages

Methods

Objectives and treatments
- To demonstrate the efficacy of:
  - 2 regimens of T1225 1.5% administered in each eye twice daily:
    For 2 days for 2-day Group,
    For 3 days for 3-day Group,
  - In comparison to a reference product (a single dose of oral azithromycin (AZM) 20 mg/kg, Zithromax®, for AZM Group),
    For the treatment of active trachoma in the concerned paediatric population and
- To assess the safety of the tested product.

Study Design
Randomised, double-masked, double-dummy, parallel-group, non-inferiority study of T1225 eye drops versus reference product.

Study population / Sample size
- Children aged ≥ 1 year and ≤ 10 years,
- With active trachoma graded either as:
  TF+TI0 (trachomatous inflammation follicular) or

Assessor’s comments:
The study No LT1225-PIII-06/06 Algeria was performed in 2008 and the MAH included into this submission. It is assessed in this report.
The study No LT1225-PIV-05/07 is expected to be finalised in 2011 and the MAH will submit the report according to article 46 of paediatric regulation.
TF+TI+ (trachomatous inflammation follicular and intense)
using simplified World Health Organization (WHO) grading scale.

Among the 670 included patients, 47 (7%) patients aged 1-2 years (all from Guinea):
- 13 in the 2-day Group,
- 14 in the 3-day Group,
- 20 in the AZM Group.

**Statistical methods**
Principal statistical hypothesis:
T1225 non-inferior to Oral AZM for primary efficacy variable. Non-inferiority margin of 10% was chosen in accordance with studies of infectious diseases with high cure rates. Evaluation based upon a 2-sided 95% confidence interval (CI) on difference in cure rate (T1225 minus Oral AZM). T1225 considered non-inferior to Oral AZM if lower limit of interval not below -10%.

Estimating treatment effect: controlling for country and other covariates (age, gender, household treatments, environmental risk factors, baseline trachoma severity, baseline Chlamidia PCR). For each prognostic factor, logistic regression was applied.

**Results**

**Recruitment / Number analysed**

Guinea Conakry: 7698 children were screened in villages, 848 had active trachoma
Pakistan: 4300 children were screened mainly in schools, 120 had active trachoma
600 patients planned, 670 patients were included and randomized: 224 into 2 days group, 225 into 3 days group, and 221 into AZM group.

In the Total Set, 644 patients (96.1%) completed 2-month study; most common reason for discontinuation = patient moved to another region. No patient discontinued due to lack of efficacy and only 1 patient discontinued due to AE (unrelated to study product). In the Intention to Treat Set, > 99% of patients received all planned doses.

**Baseline data**

Intention to Treat Set: 327 males (49.8%) and 329 females (50.2%). Mean ± SD age was 5.07 ± 2.53 years (range 1-10 years). More males in Pakistan (66%) than Guinea (46%).
Patients older in Pakistan than Guinea: mean age 7.0 vs 4.7 years.
The 2 participating countries were different from an ethnic and socio-economic point of view, explaining the differences noted at baseline. Furthermore in Guinea over 80% of the mothers were treated with AZM.

Twenty-three percent (23%) of patients were microbiologically-positive at baseline.
Trachoma grades were well balanced between groups. Trachoma in both eyes was slightly more severe in Guinea than Pakistan.
In the Intention to Treat Set, 152 patients (23%) had a positive bacteriological result in at least one eye at baseline.

**Efficacy results**

Primary Efficacy Variable: Clinical Cure Rate in Per Protocol Set:

In the Per Protocol Set, clinical cure in the worse eye at the end of the study was:
- 93.0% in the 2-day Group,
- 96.3% in the 3-day Group,
- 96.6% in the AZM Group.

In conclusion, T1225 1.5% eye drops topically applied twice daily for 2 or 3 days were demonstrated to be non-inferior to a single oral 20 mg/kg dose of azithromycin for the treatment of trachoma in children.
Safety results

There were no treatment-related AEs. There was only 1 systemic AE, and this was unrelated to the study medication (death, head traumatism). The acceptability upon instillation of T1225 was very good and similar to that of placebo eye drops in this double-dummy study.

Assessor’s comments:
This randomised, double-masked, double-dummy study included 670 children aged ≥ 1 year and ≤ 10 years.
This study was a pivotal Phase III study supporting the original registration. Although there was no statistical difference, lower cure rates were observed in the low-regimen group (2days only) and the approved SmPC posology is the 3-day therapy.
The study is described in the approved SmPC’s section 5.1.
Study No. LT1225-PIII-06/06: Clinical Efficacy and Safety assessment of T1225 Eye Drops 1.5% (Instilled Twice Daily for 3 Days) in Treatment of Active Trachoma in School Children.

Description

The study was designed and conducted between January and May 2008, in accordance with globally accepted standards of Good Clinical Practice (GCP), applicable guidelines, the Declaration of Helsinki (2000) and local regulations.

Investigation Centres: 2 wilayas (districts) in South east of Algeria (Ouargla, Ghardaïa).

Methods

Objective and treatment
To confirm T1225 1.5% efficacy, with safety assessment, in patients presenting Trachomatous Inflammation-Follicular (grade TF) or Trachomatous Inflammation - Follicular and Intense (grade TI) at Day 0. The T1225 1.5% eye drops, administered in each eye twice a day for 3 days.

Study design
Phase III study, bicentric, open, 1 treatment group.

Study population / Sample size
School children aged ≥ 6 years and ≤ 15 years
A total of 326 patients were analysed, including 322 children.

Statistical methods
No statistical hypothesis on sample size was tested for this study with a treatment group.

Descriptive statistics: The type I error α was considered at 5% (two-sided) for all the tests and the confidence intervals presented.

Quantitative: number of observed values, mean, median, standard deviation, minimum and maximum.

The clinical efficacy was mainly estimated on the worse eye.

No Statistical tests were performed

Results

Recruitment / Number analysed
3127 children aged 6-19 years were screened in 19 different schools. 700 children were diagnosed with active trachoma, the first 326 patients were included in the study.

Number of patients per set: 326 in Included Set, 326 in Safety Set, 315 in Full Analysis Set (FAS), 296 in Per Protocol Set. In the Safety Set, 282 patients completed the study; the most common reason for discontinuation was patients did not come for the visit on Day 84. No patient discontinued due to lack of efficacy and 5 patients discontinued due to AE (unrelated to study product). In the Included Set, more than 95% of patients received all planned doses.

Baseline data
IS: 190 boys (58.28%) and 136 girls (41.72%). Mean ± SD age was 11.4 ± 4.4 years with 50.92% of the children ranged from 10 to 15 years (11.66% of the patients older than 15 year old: 34 children aged 16 to 18 years and 4 adults). The Included Set and Full Analysis Set were similar at baseline for all demographic characteristics.

Mean visual acuity in the worse eye was 8 ± 2. This value was similar for each eye and for the Full Analysis Set. For left and right eyes, the trachoma grades were similar at baseline.

Efficacy results
Primary efficacy variable: the clinical cure in the worse eye (at the end of the study, at D84).
In the Full Analysis Set, cure at the end of the study was reported for 286 patients (90.79%).
These findings were similar for the Per Protocol Set (92.57% of patients).
The percentage of children cured at the end of study increased with the age of the patients:
86.2% for 6 to 10 years old, 91.9% for 10 to 15 years old and 100% for children older than 15 years. The percentage of children cured at the end of study was similar for boys and girls (more than 90%).
In conclusion, in Per Protocol Set, T1225 1.5% eye drops given for 3 days were demonstrated to be efficient for 92.6% of patients whatever their trachoma grade at baseline, sex and town.

Safety results
10 AEs were considered to be treatment-related but no serious ocular or systemic AEs were reported. However, it should be remembered that the protocol was designed as a field study in a large number of subjects, and that the patients were all children aged from 6 to 15 years. The acceptability upon instillation of T1225 eye drops was good.

Assessor’s comment
This open, one treatment study was performed in 2008 according to the approved SmPC’s indication and posology. 322 school children (6 years and older) received azithromycin eye drops.

The safety and efficacy results further support the approved indication and posology and do not affect the present risk-benefit assessment.
Purulent Bacterial Conjunctivitis Indication

Study No. LT1225-PIII-11/03: Clinical Efficacy and Safety of T1225 1.5% Eye Drops (3-Day Treatment) versus tobramycin 0.3 % Eye Drops (7-Day Treatment) in the Treatment of Purulent Bacterial Conjunctivitis

Description
The study was designed and conducted between 25 May 2004 and 24 June 2005, in accordance with globally accepted standards of Good Clinical Practice (GCP), applicable guidelines (in particular CPMP/ICH/2711/99 and CPMP/EWP/462/95 for clinical trials in children, and CPMP/EWP/558/95 for the treatment of bacterial infections), the Declaration of Helsinki (2000) and local regulations.

Investigation Centres : 54 centers in 8 countries
European countries: Bulgaria, France, Portugal, and Romania,
Countries outside Europe: Guinea, India, Morocco, and Tunisia

The paediatric subset was analysed and the article „Efficacy and Safety of Azithromycin 1.5% Eye-drops for Purulent Bacterial Conjunctivitis in Pediatric Patients“ was accepted for publication at the time of submission.

Methods

Objective
To demonstrate the efficacy of T1225 1.5% eye drops, in comparison to reference product, for the treatment of purulent bacterial conjunctivitis, and to assess the safety.

Treatment
1. T1225 1.5%: 1 drop instilled in lower conjunctival sac of each eye twice daily for 3 days.
2. Tobramycin (Tobrex®) 0.3% preserved eye drops in a multi-dose bottle. 1 drop instilled in each eye every 2 hours while awake (up to 8 times per day) for 2 days, then 1 drop in each eye 4 times daily for 5 days.

Study design
Multicentre, international, investigator-masked, randomised, parallel-group, non-inferiority study of T1225 eye drops versus reference product.

Study population / Sample size
- ≥ 1 day old (newborn, infant, child, adult); with
- Unilateral or bilateral purulent bacterial conjunctivitis defined as:
  - bulbar conjunctival injection (mild, moderate, or severe)
  - conjunctival purulent discharge (mild, moderate or severe).

Randomised population:
A total of 1,043 patients were selected and randomised for the study by 40 centers from 8 countries: 372 India, 297 Tunisia, 113 Bulgaria, 83 France, 83 Guinea, 13 Morocco, 78 Romania, 4 Portugal.
A total of 150 patients under 18 years old were included:
  - 73 (13.9%) in the T1225 Group,
  - 77 (14.8%) in the Tobramycin Group.
A total of 109 children under 12 years old were included:
  - 50 (9.5%) in the T1225 Group,
  - 59 (11.4%) in the Tobramycin Group.
A total of 38 infants between 28 days and 23 months old were included:
  - 13 (2.5%) in the T1225 Group,
25 (4.8%) in the Tobramycin Group. 
A total of 5 newborns between 0 days and 27 days old were included: 
  3 (0.6%) in the T1225 Group, 
  2 (0.4%) in the Tobramycin Group.

Statistical methods
Principal statistical hypothesis:
T1225 non-inferior to tobramycin for primary efficacy variable.
Non-inferiority margin of 10% was chosen in accordance with studies of infectious diseases with high cure rates. Evaluation was based upon a 2-sided 95% confidence interval (CI) on difference in cure rate (T1225 minus tobramycin).
Estimating treatment effect:
controlling for country and other covariates (causative organism category, *Staphylococcus epidermidis* as main causative organism, age category, childhood [< 12 years old], disease severity at baseline, number of days between last instillation and D9).

Results

Recruitment / Number analysed

Inclusion criteria have been chosen in order to include a wide population of patients from newborns to elderly. 
In the Intention to Treat Set there were 539 males (51.7%) and 504 females (48.3%). The overall mean ± SD age of the patients was 39.0 ± 20.7 years, ranging from 4 days old (newborn) to 87 years.
The Safety Set consisted of a total of 1,015 patients: 508 patients in the T1225 group and 507 patients in the tobramycin group.

Baseline data

At D0 in the worse eye in the Intention to Treat Set, bulbar conjunctival injection was mild in 21%, moderate in 59%, and severe in 20% of patients. Conjunctival purulent discharge was mild in 30%, moderate in 52%, and severe in 18% of patients. There were no notable differences between the treatment groups with respect to clinical ocular signs and symptoms.
521 patients (50%) in the Intention to Treat Set had positive bacterial samples in the worse eye. There were no notable differences in germ distribution between the treatment groups at baseline.

Amongst the 150 children, 58 (39%) had positive cultures at Day 0: 25 patients in azithromycin group and 33 patients in tobramycin group. The germ distribution was slightly different with a higher prevalence of *Haemophilus* (36%) and *Streptococcus pneumoniae* (10%).

Efficacy results in the total study population

Primary efficacy variable: clinical cure at the Test of Cure visit on Day 9 ± 1, in the worse eye for patients with positive cultures at Day 0, results:
  87.8% in the T1225-Group after 6 instillation per treated eye, 
  89.4% in the Tobramycin-Group.

The cure rate difference between both groups was: -1.6 % (2-sided exact 95% CI [-7.5;4.4]). The lower limit of this interval was not below -10%. Thus T1225 was demonstrated to be non-inferior to tobramycin for the primary efficacy variable.

Efficacy results in children

In the paediatric population, clinical efficacy appeared to be similar to that observed in adults. Although the total number of children was low for each category, the bacteriological resolution rate appeared to be similar in children and adults.
In children the azithromycin therapy provided a greater bacteriological cure on day 3 than did tobramycin (p < 0.01) and eradicated bacteria that were defined as resistant, using classical antibiogram.

The age category was not a prognostic factor for the clinical cure.

**Safety results**

No serious treatment-related adverse events (AEs) were reported during the study and therefore, in the pediatric population.

One patient (17 years old) in the azithromycin group presented symptoms upon instillation (itching/burning/stinging, foreign body sensation, and blurred vision) versus two patients (10 and 17 years old) in the tobramycin group (itching/burning/stinging; itching/burning/stinging and stickiness). The ocular surface safety profile of both studied products was satisfactory since no impairment was observed at the slit lamp examination.

This safety profile on Day 3 was rated by the investigator as satisfactory/very satisfactory for 96% of cases in azithromycin group and for 92% of the cases in tobramycin group. At Day 9, 97% of children or relatives assessed azithromycin as comfortable versus 94% of the cases in tobramycin group.

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**Assessor’s comments**

This multi-center, randomized, investigator-masked, parallel-group study included a subset of 150 children, 73 received azithromycin including 3 newborns and 13 infants and toddlers (28 days to 23 months of age).

This study was a pivotal Phase III study supporting the original registration and Section 5.1 of the SmPC provides information from this clinical trial.

The results of paediatric subset was published in Pediatr Infect Dis J 2010;29:222-6 "Efficacy and Safety of Azithromycin 1.5% Eye-drops for Purulent Bacterial Conjunctivitis in Pediatric Patients".

This article was included into the assessment of tobramycin FI6W/002/pdWS/001 procedure as well.

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**3. Discussion on clinical aspects and conclusion**

Since the first launch of Azyter eye drops in Europe, on 15 February 2008 four PSURs were submitted. The MAH received 9 spontaneous reports of medically confirmed adverse reactions and one report from Portuguese Authorities. Among all reported cases one concerned a child (Portuguese Authorities’ one): 3-year old female patient, localized skin reaction, unspecified indication of treatment, completely recovered.

Altogether 843 children were treated with T1225 1.5% in the three clinical studies submitted. Azyter eye drops have the advantage of a low dosing regimen of 1 drop instilled in each eye twice daily for 3 days (compliance, rapid control of infection) and of single dose formulation free of benzalkonium chloride.

In conclusion, the available efficacy and safety data of Azyter eye drops do not indicate any need for re-evaluation of the positive benefit – risk assessment for the use in paediatric patients.
Overall conclusion

The data presented by the MAH do not reveal any new information on the safety and efficacy for the use of Azyter for the paediatric population. The assessor however noticed that there is a need to update the product information according to the current SmPC guideline as follows:

4.1 Therapeutic indication
The target population should be defined. The following wording is suggested:
“…
- Purulent bacterial conjunctivitis in adults and children aged 2 years and older,
- Trachomatous conjunctivitis caused by Chlamidia trachomatis in adults and children aged 1 year and older.
…”

5.1 Pharmacodynamic properties
Paediatric population subheading should be added and information from clinical trials should be provided under this subheading. Information should be updated when new relevant information becomes available, information and results of confirmatory studies should be provided. The following wording is suggested:
…”Azyter was evaluated in a bicentiric, open label, one treatment group confirmatory study to assess the efficacy of topical treatment of 2 instillations per day for 3 days in school children with active trachoma. 322 children aged 6-15 years were included. Azyter was demonstrated to be efficient for 92,6% of patients independent of their trachoma grade at baseline, sex or location. The acceptability of the treatment in the community setting was considered to be good.”

Recommendation

The information and results of the new, confirmatory study should be provided in section 5.1 of the SmPC. The assessor noticed that there is a need to update the product information according to the current SmPC guideline as well.

An appropriate variation to be requested from the MAH within 90 days of completion of this procedure to update the product information according to the current guideline (section 4.1 and 5.1 and when relevant other sections).

Request for supplementary information

“... considering the current off-label use of azithromycin for the prophylaxis of ophthalmia neonatorum on the basis of available data on pharmacology and gonococcal microbiologic sensitivity, it would be worth asking the Applicant to collect relevant clinical efficacy and safety data to enable formally supporting such a use.”
VI. MAH’S RESPONSE TO QUESTIONS

Since the start of the assessment of this article 45 procedure, two new clinical studies including children were ended beginning of 2011.

1) LT1225-PIIIB-02/08: Clinical Efficacy and Safety of Azyter® (Azithromycin 1.5%) versus Tobramycin 0.3 % in the Treatment of Purulent Bacterial Conjunctivitis of children.

And

2) LT1225-PIV-05/07 (CM): Clinical efficay assessment of AZYTER® (T1225) antibiotic eye drops (1 instillation twice a day during 3 days) in curative and preventive Trachoma mass treatment in a North Cameroun population

The MAH informed accordingly the Paediatric Committee via Article 46 procedure on August 2011 of they wish to propose a change of the Product Information based on the result of these two above mentioned studies. The MAH received on December 05th 2011 the response: “Please be informed that for the worksharing procedure concerning studies submitted in accordance with Article 46 of the Regulation No 1901/2006, as amended, Netherlands has been appointed as Rapporteur for Azyter (azithromycin dichydrate). The Rapporteur considers that for the moment there is no need to submit the paediatric data to start a worksharing procedure. Confirmation has been received that the paediatric study will be assessed as part of an upcoming variation.”

In accordance with the RMS (NL) the MAH submitted end of January 2012 a type II variation (NL/H0855/01/II/10) in order to include these two studies in the MA file of AZYTER and to modify the Product Information.

The MAH would like to enlarge the paediatric indications of AZYTER as follows:
4.1 Therapeutic indications

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.

4.2 Posology and method of administration

**Posology**

*Adults, Adolescents (12 to 17 years), children (2 to 11 years)*:
Instil one drop in the conjunctival fornix twice a day, morning and evening, during three days.

It is unnecessary to prolong treatment beyond three days.

Adherence to the dosing regimen is important for the success of treatment.

*Children (1 to 2 years)*
For trachomatous conjunctivitis, no dose adjustment is necessary.
For purulent bacterial conjunctivitis, there is no sufficient experience with Azyter in children younger than 2 years of age (see section 5.1).

*Children (less than 1 year)*
There is no sufficient experience with Azyter in children younger than 1 year of age for trachomatous conjunctivitis as well as for purulent bacterial conjunctivitis (see section 5.1).

**Elderly patients:**
No dose adjustment is necessary.

**Paediatric population**

*AZYTER* eye drops may be used in paediatric patients (from term newborn infants to adolescents). No dose adjustment is necessary.

The timetable given by the RMS is the following:

Day 0: 14.02.2012
Day 85: 09.05.2012
Day 90: 14.05.2012

**In conclusion the comments of the MAH are the following:**

4.1 Therapeutic indication

The MAH disagrees with the Rapporteur’s comment as a type II variation is still under assessment in order to enlarge the paediatric indication. Therefore this request is not yet relevant
but the MAH agrees to update this section accordingly to the decision of the RMS at the variation procedure NL/H/0855/01/II/10.

5.1 Pharmacodynamic properties

The MAH agrees with the Rapporteur to add this information in this section.

VII: MEMBER STATES’ OVERALL CONCLUSION AND RECOMMENDATION

Draft decision (day 90) of the updated FPdAR

The Applicant’s response is acceptable. The ongoing variation procedure resolves the issues. HU is not among CMSs therefore the MAH is requested to provide the approved SmPC of the variation to include into Public pdAR (day 180 of this procedure) to provide the latest approved information on the product. No SmPC and PL changes are proposed as a result of this procedure. No further action is required.

Day 115 MS’s comments

MSs agreed with the Rapporteur’s conclusion, one MS had some additional points for consideration before adopting final recommendation for the SmPC:

The UK acknowledges the MAH’s ongoing type II variation application (NL/H/0855/01/II/10) to enlarge the paediatric indication and to include information from the recently finished two paediatric clinical trials (LT1225-PIIIB-02/08 and LT1225-PIV-05/07 (CM). However, the UK is of the view that some confusion occurred between the variation and this paediatric work-sharing procedure: The UK notes that an additional study (LT1225-PIII-06/06) has been assessed as part of the paediatric work-sharing procedure. If the Rapporteur concludes that this work-sharing procedure does not result in any SmPC changes while awaiting the completion of the ongoing type II variation, the information from study LT1225-PIII-06/06 will not be included in section 5.1 of the SmPC at all. This inclusion has been agreed by the member states and the MAH as well (page 21 of FAR) as part of this paediatric work-sharing procedure.

In summary, the UK is in agreement with the Rapporteur that the ongoing variation will resolve the issue regarding the paediatric indication age groups and therefore the update of section 4.1 of the SmPC can await the outcome of the type II variation procedure. However, the UK is of the view that the earlier proposed wording summarizing study LT1225-PIII-06/06 should be included in section 5.1 of the SmPC as the outcome of this European paediatric work-sharing procedure.

“5.1 Pharmacodynamic properties

Azyter was evaluated in a bicentric, open label, one treatment group confirmatory study to assess the efficacy of topical treatment of 2 instillations per day for 3 days in school children with active trachoma. 322 children aged 6-15 years were included. Azyter was demonstrated to be efficient for 92.6% of patients independent of their trachoma grade at baseline, sex or location. The acceptability of the treatment in the community setting was considered to be good.”
Rapporteur’s comment:

The Rapporteur considered the comment of the UK and the facts below:

- NL requested to receive the LT1225-PIII-06/06 study as part of this procedure and the MAH sent it to NL on September 30, 2009,

- among D85 comments on 5.1 were:
  “…However, information from clinical trials in section 5.1 are generally not accepted for antibiotics…”
  “…according to the forthcoming revision of the EU guideline the section 5.1 should not detail clinical studies unless negative data…”,

- D115 comments: MSs including the RMS (NL) of the ongoing type II variation agree with the updated D90 FPdAR’s conclusion that no SmPC changes recommended as a result of this art. 45 procedure,

- The information from phase III study assessed in this procedure came from 326 school children before 2008.

- The information from later confirmatory phase IIb and phase IV studies assessed in the ongoing type II variation came from much larger studies (e.g.: LT1225-PIV-05/07; 100 000 people with trachoma, including children of all ages, covering the school age group as well).

Therefore the Rapporteur is of the view that the RMS of the ongoing type II variation has all study’s data. The results of these studies will be assessed and the approved SmPC will include the information definitely from the latest confirmatory studies which covered the age group of the study under evaluation in this procedure. So no information will be lost.

FINAL POSITION (DAY 120)
No SmPC and PL changes are proposed as a result of this procedure. No further action is required.
VII: LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORITY HOLDERS INVOLVED

MAH: Laboratories Théa

Current registration status
The registration in Europe of AZYTER 1.5 mg/g, eye drops, solution was performed aim to a decentralised procedure NL/H/855/01/DC ended on 30 July 2007 in the following countries:

<table>
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<th>Country</th>
<th>Action-Date</th>
<th>Launch date</th>
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<td>ITALY</td>
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<td>-</td>
<td>AZYTER®</td>
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<td>PORTUGAL</td>
<td>A-27 Nov. 2007</td>
<td>Aug. 2008</td>
<td>AZYTER®</td>
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<td>SPAIN</td>
<td>A-17 Jan. 2008</td>
<td>01 Jan. 2009</td>
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<td>AZYTER®</td>
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<td>POLAND</td>
<td>A-06 Nov. 2007</td>
<td>Apr. 2008</td>
<td>AZYTER®</td>
</tr>
</tbody>
</table>

Since the initial submission regarding Azithromycin article 45, a repeat use (NL/H/855/01/E/01) was performed for Bulgaria, Cyprus, Czech Republic, Denmark, Greece, Finland, Ireland, Norway, Romania, Sweden, Slovak Republic and United Kingdom which was positively ended on 21/02/2011.