HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

30 April 2008

AZYTER 15 mg/g, eye drops in single dose container
Box of 6 single-dose containers (CIP: 382 038-2)

Applicant: THEA

Azithromycin

List I

Marketing authorisation (MA) date: 24 October 2007 (decentralised procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient:

Azithromycin

1.2. Background

AZYTER is the first macrolide antibiotic eye drop and the first antibiotic eye drop available in single dose containers.

1.3. Indication

“Local antibacterial treatment of conjunctivitis caused by susceptible microorganisms:
- Purulent bacterial conjunctivitis
- Trachomatous conjunctivitis due to *Chlamydia trachomatis*

Official guidelines on the appropriate use of antibacterial drugs should be taken into consideration.”

1.4. Dosage

Posology
Adults, adolescents (aged 12 to 17 years), children (aged 2 to 11 years):
Instill 1 drop into the conjunctival cul-de-sac twice daily, morning and evening, for 3 days.
Treatment need not be continued for more than 3 days .
It is important to respect the dosage for treatment to be successful.

Children aged from 1 to 2 years.
No dose adjustment is necessary in trachomatous conjunctivitis.
For purulent bacterial conjunctivitis, there is insufficient experience on the use of AZYTER in children under the age of 2 years.

Infants (aged less than 1 year):
For trachomatous conjunctivitis and purulent bacterial conjunctivitis, there is insufficient experience on the use of AZYTER in children under the age of 1 year.

Elderly patients:
No dosage adjustment is required.

Method of administration
Ophthalmic route.
Give the patient the following instructions:
- Carefully wash the hands before and after instillation
- Avoid touching the eye or the eyelids with the tip of the container
- Discard the container after use.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

S : Sensory organs
S01 : Ophthalmic medicines
S01A : Anti-infectives
S01AA : Antibiotics
S01AA26 : Azithromycin

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparable medicines

AZYTER is the only antibiotic eye drop belonging to the macrolide class.

2.2.2. Not strictly comparable medicines

AZYTER is the only antibiotic eye drop indicated both in purulent bacterial conjunctivitis and trachoma.

2.3. Medicines with a similar therapeutic aim

These are other antibiotic eye drops indicated in bacterial conjunctivitis of the external structures of the eye and annex due to susceptible microorganisms:

- Aminosides:
  - gentamicin: GENTALLINE, GENTAMICINE CHAUVIN, MICROPHTA (not marketed)
  - tobramycin: TOBREX
- Rifampicin: RIFAMPICIN
- Fusidic acid: FUCITHALMIC

Fluoroquinolones and antibiotic combinations are used in severe conjunctivitis or as second-line treatment.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The applicant provided 2 phase III efficacy studies:

- a non-inferiority study versus 0.3% tobramycin eye drops in patients with purulent bacterial conjunctivitis (study LT1225-11/3)
- a non-inferiority study versus 0.3% azithromycin per os in patients with trachoma (study LT1225-10/3).

- Purulent conjunctivitis study versus 0.3% tobramycin eye drops

Randomised, investigator-blind, non-inferiority study comparing azithromycin 1.5% eye drops with 0.3% tobramycin eye drops in newborn infants (>1 day), children and adults with purulent uni- or bilateral bacterial conjunctivitis defined by:

- mild (grade 1), moderate (grade 2) or severe (grade 3) bulbar conjunctival erythema

AND

- mild, moderate or severe purulent secretion.

The bacterial origin of the conjunctivitis was determined on a sample.

Patients with a suspected viral infection, major risk factors for severe complications (in particular ocular trauma and foreign bodies), bacterial conjunctivitis diagnosed more than 7 days before inclusion, dacryocystitis, corneal ulceration, keratitis or any ocular abnormality were excluded.

The patients received either:
- azithromycin 1.5% eye drops at a dose of 1 drop in the morning and 1 drop in the evening for 3 days, or
- tobramycin 0.3% eye drops at a dose of 1 drop every 2 hours for 2 days then 4 times daily for 5 days.

The primary endpoint was the percentage of patients obtaining a clinical cure of the most affected (worse) eye at D9 (±1):
- no bulbar conjunctival injection
- no purulent secretion

Cure of the worse eye at D3 was a secondary outcome variable.
Azithromycin eye drops could be considered non-inferior to tobramycin eye drops if the lower limit of the 95% confidence interval of the difference between treatments was greater than -10% defined as non-inferiority threshold.

Results:

A total of 1043 patients were included in the study including 524 in the azithromycin eye drops group and 519 in the tobramycin eye drops group (intention-to-treat population = ITT).
The per protocol population (PP) defined by the patients with positive bacteriological results at D0 and with no major deviation from the protocol comprised 245 patients on azithromycin and 226 patients on tobramycin.

Most patients were adults (mean age 39 years, 150 were aged under 18 years including 5 new-born babies aged between 0 and 27 days and 38 infants between 28 days and 23 months).
The conjunctivitis was mild in 20 to 30% of cases, moderate in 50 to 60% of cases and severe in 20% of cases.

At baseline, 521 patients (i.e. 50%) had a positive bacteriological test result for the “worse” (most affected) eye. The distribution of the most frequent bacteria was:
- *Staphylococci*: *Staphylococcus epidermidis* (38% of patients), other coagulase-negative Staphylococci (22%), and *Staphylococcus aureus* (17%)
- *Haemophilus* (7%), *Streptococcus pneumoniae* (6%)
- other Gram-negative bacteria: *Enterobacteriaceae* (6%), and *Acinetobacter* (5%)

The percentages of patients with a clinical cure at D9 “in the worse eye” are given in table 1.

Table 1: Clinical cure at D9 in the worse eye (study LT1225-11/3)

Population	**Patients with a clinical cure on the worse eye at D9**		
	Azithromycin N (%)	**tobramycin N (%)**	**Difference (%) $CI_{95\%}$**
PP	215 / 245 (87.8)	202 / 226 (89.4)	-1.6 [-7.5; 4.4]
ITT	447 / 524 (85.3)	440 / 519 (84.8)	0.5 [-3.8; 4.9]

As in both the PP population and ITT population, the lower limit of the 95% confidence interval of the difference between treatments was above the predefined non-inferiority threshold (- 10%), azithromycin eye drops were considered to be non-inferior to tobramycin eye drops in terms of percentage of patients with clinical cure of the worse eye at D9.

The non-inferiority between treatments was also observed at D3: 28.8% with azithromycin versus 18.6% with tobramycin hence a difference of 11.2% with a 95% CI of [3.4%; 18.9%].

Trachoma: study versus oral azithromycin (study LT1225-10/3)

Randomised, double-blind, double-placebo, non-inferiority study comparing the efficacy of azithromycin 1.5% eye drops with that of oral azithromycin (indication not validated by the MA but recognised by WHO and the Afssaps recommendations for the treatment of trachoma) in children aged from 1 to 10 years with trachomatous conjunctivitis caused by *Chlamydia trachomatis*. The study was conducted in Guinea and Pakistan.

Children had to have active trachoma defined according to WHO[1] by:
- follicular inflammatory trachoma (TF)

or
- intense inflammatory trachoma and follicular inflammatory trachoma (TF + TI)

Children with trachoma-related complications, i.e. trichiasis (grade TT+), corneal opacity (grade CO+) or tarsal conjunctival fibrosis with eyelid deformity requiring surgery were not included.

The patients received one of the following treatments:
- azithromycin 0.3% eye drops: 1 drop in the morning and 1 drop in the evening for 2 days (instead of the 3 days for the dosage validated by the MA)
- azithromycin 0.3% eye drops: 1 drop in the morning and 1 drop in the evening for 3 days
- oral azithromycin: a single dose of 20 mg/kg (dosage recommended by WHO).

The primary efficacy endpoint was the percentage of patients with a cure in the worse eye on D60 (± 3 days), where a cure was defined by the presence of less than 5 follicles of at least 5 mm in diameter on the upper tarsal conjunctiva (grade TF0 according to the WHO classification).
The cure of the worse eye at D30 was a secondary endpoint.

Azithromycin eye drops could be considered non-inferior to oral azithromycin if the lower limit of the 95% confidence interval of the difference between treatments was greater than -10% defined as non-inferiority threshold.

Results:

A total of 670 patients was included in the study i.e. 449 in the azithromycin eye drops group and 221 in the oral azithromycin group (ITT Intention-to-treat population).
The PP (per-protocol) population defined by patients with no major deviation from the protocol comprised 389 patients on azithromycin eye drops and 179 patients on oral azithromycin.

The average age of included children was 5 years and their trachoma was grade TF+T10 in the worse eye in 80% of the cases and grade TF+T1 in 20% of cases.

[1] WHO Classification of trachoma:
TF : follicular inflammatory trachoma: conjunctivitis
TI : intense inflammatory trachoma
TS : scarring trachoma
TT : trachomatous trichiasis (rubbing of lashes on cornea)
CO : corneal opacity progressing to blindness:

There were 112 randomised children with *Chlamydia*-positive bacteriological results in at least one eye in the azithromycin eye drop groups and 40 in the oral azithromycin group.

The percentages of patients with a clinical cure at D60 in the worse eye are given in table 2. The results for the group treated with azithromycin eye drops for 2 days are not presented below as this dosage is not recommended by the MA.

Table 2: Clinical cure at D60 in the worse eye for the PP population (study LT1225-10/3)

Population	Patients with a clinical cure in the worse eye at D60		
	Azithromycin eye drops (3 days) n/N (%)	Oral azithromycin n/N (%)	Difference (%) $CI_{95\%}$
PP	183 / 190 (96.3)	173 / 179 (96.6)	-0.3 [-4.6; 3.9]
ITT	211 / 220 (95.9)	205 / 214 (95.8)	-0.1 [-4.1; 4.3]

As in both the PP population and the ITT population, the lower limit of the 95% confidence interval of the difference between treatments was above the predefined non-inferiority threshold (-10%); azithromycin eye drops were considered to be non-inferior to oral azithromycin in terms of percentage of patients with a clinical cure of the worse eye at D60.

The non-inferiority between treatments was also found on D30 (secondary study outcome variable): 91.4% with azithromycin versus 95.3% with oral azithromycin, i.e. a difference of 3.9% with a $CI_{95\%}$ [-9.5%; 1.6%].

3.2. Safety

In clinical studies, the safety of azithromycin was good and similar to that of the comparators (tobramycin eye drops and oral azithromycin). The most frequent adverse events (≥1/10) were burning and tingling sensations on instillation.

3.3. Conclusion

In serious purulent conjunctivitis, azithromycin 1.5% eye drops (2 drops per day for 3 days) were compared with tobramycin 0.3% eye drops (1 drop every 2 hours for 2 days then 4 times daily for 5 days) in a randomised, single-blind study. Included patients were aged from 1 day and had purulent uni- or bilateral bacterial conjunctivitis. Azithromycin 1.5% eye drops were non-inferior to tobramycin 0.3% eye drops in terms of clinical cure of the worse eye at 9 days.

In trachoma, azithromycin 1.5% eye drops (2 drops per day for 3 days) were compared with a single oral dose of 20 mg/kg azithromycin (treatment recommended by WHO and Afssaps but without an indication validated by MA in trachoma) in a randomised, double- blind, double-placebo study conducted in Guinea and in Pakistan. Included patients were children aged from 1 to 10 with moderate (TF) to severe (TF + TI) *Chlamydia trachomatis* conjunctivitis. Azithromycin 1.5% eye drops were non-inferior to oral azithromycin in terms of clinical cure of the worse eye at 60 days.

Azithromycin eye drops were well tolerated in these studies. The most frequent treatment-related adverse events were ocular discomfort during instillation.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

4.1.1. Purulent bacterial conjunctivitis

Conjunctivitis is inflammation of the conjunctiva, with no corneal involvement. A bacterial aetiology is demonstrated by the presence of purulent secretions.
The criteria of seriousness of purulent bacterial conjunctivitis are:
- copious purulent discharge
- chemosis (conjunctival oedema)
- palpebral oedema
- excessive tearing
- impaired vision and even moderate visual acuity loss
- photophobia.

Progression to keratitis may cause blindness or even purulent panophthalmitis.

This proprietary drug is intended to provide curative treatment.

Public health benefit:

Despite its incidence and repercussions on quality of life, purulent bacterial conjunctivitis represents a low public health burden because it only rarely has complications (keratitis, blindness).
Improved management of these clinical conditions is not an established public health priority.
A review of the available data shows that AZYTER is not expected to have an additional impact in terms of morbidity and quality of life compared to the other local treatments.
Accordingly, in the current state of knowledge and taking into account other therapies available at this time, AZYTER is not expected to benefit public health in this indication.

The efficacy/safety ratio is high.

This medicine product is used for first-line therapy.

There are alternative treatments.

The actual benefit of AZYTER 15 mg/g, eye drops in single dose containers, is substantial in this indication.

4.1.2. - Trachomatous conjunctivitis due to *Chlamydia trachomatis*

Trachoma is chronic granular conjunctivitis due to *Chlamydia trachomatis* (serovars A to C). It is defined by:
- conjunctival follicular hyperplasia;
- corneal neovascularisation;
- exacerbations followed by remissions;
- cicatricial retraction of the conjunctiva, cornea and eyelids.

After years of repeated re-infection, sclerosis of the inner eyelid occurs and causes the eyelid to fold inwards (entropion) so that the lashes rub against the eyeball (trichiasis) and in particular the cornea.
In the absence of surgical treatment, corneal opacities develop and progress to irreversible blindness.
Blindness due to trachoma generally occurs after 15 to 20 years of disease progression.

This medicine product is intended to provide curative treatment.

Public health benefit:

Trachoma represents a low public health burden as it is uncommon in Metropolitan France.

Improved management of this disease is not an established public health priority.

A review of the available data shows that AZYTER is not expected to have an additional impact in terms of morbidity and quality of life compared to oral azithromycin.

Accordingly, in the current state of knowledge and taking into account other therapies available at this time, AZYTER is not expected to benefit public health in this indication.

The efficacy/safety ratio is high.

This medicine product is used for first-line therapy. However, in the context of Metropolitan France, the role of azithromycin eye drops is limited and oral azithromycin should remain the reference treatment.

There are alternative treatments but the indication in trachoma is not validated by the MA.

The actual benefit of AZYTER 15 mg/g eye drops in single dose containers, is substantial in this indication.

4.2. Improvement in actual benefit

AZYTER 15 mg/g, eye drops in single dose containers, does not improve the actual benefit (IAB level V) in the management of purulent bacterial conjunctivitis and trachoma.

4.3. Therapeutic use

4.3.1. Reference treatment strategy

- **Purulent bacterial conjunctivitis**[2]

Antibiotics shorten the duration of symptoms of bacterial conjunctivitis, but their effect at 8 days is not significantly better than that of a placebo (Grade A).
This gain in individual comfort should be weighed against the risk of selecting strains resistant to certain antibiotics. The benefit-risk ratio would then be reversed at community level. Hence, in the absence of criteria of seriousness or risk factors, an antibiotic should not systematically be used. Bacterial conjunctivitis should be treated firstly by irrigation with physiological saline containing a disinfectant and antibiotic treatment should be reserved for serious forms.
However, in certain specific situations such as in developing countries, local antibiotic therapy may be used to prevent the serious corneal complications that may lead to blindness.

In adults
Serious bacterial conjunctivitis with risk factors must be treated by a local antibiotic. Antibiotic therapy is then probabilistic or guided by susceptibility tests (expert consensus). Any antibiotic effective against the suspected microorganism may be prescribed. For reasons involving microbial ecology, the use of fluoroquinolones and antibiotic combinations should be restricted to “severe” forms of bacterial conjunctivitis or for second-line therapy (expert consensus).

In children
Streptococci and *Haemophilus influenzae* are the bacteria most commonly involved. Accordingly, rifamycin, active against all these bacteria, and bacitracin (marketing stopped), active against most strains of *Streptococcus pyogenes*, should be preferred.

[2] Afssaps Guidelines: Eye drops and other topical antibiotics in superficial eye infections (July 2004)

In infants, acute conjunctivitis should be treated by a local antibiotic. In the case of recurrent conjunctivitis, patients should be examined for imperforate lachrymal ducts by an ophthalmologist (expert consensus).

- ***Chlamydia trachomatis* trachoma**

Trachoma is the first cause of blindness in the world. It is an infectious disease restricted to the eye caused by *Chlamydia trachomatis* (serovars A to C) and is mainly an endemic disease in developing countries.
The prevalence of trachoma falls after oral or topical antibiotic treatment (Grade B)[2].
Oral instant treatment by azithromycin (20 mg/kg and 1 g in adults) is the reference treatment. Rifamycin may be given for second-line therapy[2].

4.3.2. Therapeutic use of the medicine product:

- **Purulent bacterial conjunctivitis**

Azithromycin eye drops are for first-line therapy in the management of serious cases of conjunctivitis requiring antibiotic therapy. AZYTER may be used in adults and children from 2 years.

- ***Chlamydia trachomatis* trachoma**

In the case of trachoma, a single oral azithromycin dose is the reference treatment (Afssaps and WHO guidelines) but this indication is not validated by the MA in France.
Although oral treatment is effective, WHO recommended the development of an azithromycin eye drop formulation, in particular to prevent the emergence of resistances due to mass antibiotic therapy and to treat children who have a moderate form of the disease and contact subjects.

According to the WHO data and recommendations, AZYTER may be considered to provide first-line therapy, more particularly in children (from 1 year) with moderate forms of trachoma and family/household contacts.

However as this disease is not endemic in Metropolitan France, there is only a low risk of emergence of resistance strains due to systemic antibiotic therapy to treat trachoma.

4.4. Target Population

Purulent bacterial conjunctivitis:
Bacterial conjunctivitis is frequent with an annual incidence of 16 cases per 1000 patients in general medicine[3].
There are no epidemiological data to assess the population of patients with purulent bacterial conjunctivitis.

Trachoma:
Trachoma is an endemic disease in developing countries so that trachomatous patients treated in France are mainly imported cases. The target population of AZYTER in this indication may be considered to be negligible.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indications and at the posology in the marketing authorisation.

The commission underlines that AZYTER is useful because of its short treatment duration of 3 days and because it spares the use of fluoroquinolones.

[3] Rietveld RP, Ter Riet G, Bindels PJE et al. Predicting bacterial cause in infectious conjunctivitis: cohort study on informativeness of combinations of signs and symptoms. BMJ 2004;329:206-10

4.5.1. Packaging

Appropriate for the prescription conditions.

4.5.2. Reimbursement rate

65%.