# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

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

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of solution contains 15 mg of azithromycin dihydrate equivalent to 14.3 mg of azithromycin.

One single-dose container of 250 mg solution contains 3.75 milligrams of azithromycin dihydrate.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Eye drops, solution in single-dose container.

Clear, colourless to slightly yellow, oily liquid.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

AZYTER 15 mg/g, eye drops, solution in single-dose container is indicated for the local antibacterial curative treatment of conjunctivitis caused by susceptible strains (see sections 4.4 and 5.1):

- Purulent bacterial conjunctivitis in children (aged from birth to 17 years) and adults
- Trachomatous conjunctivitis caused by *Chlamydia trachomatis* in children (aged from birth to 17 years) and adults (see section 4.4 “Use in neonates”).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

### 4.2 Posology and method of administration

*Posology*

Adult population

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.

Elderly patients

No dose adjustment is necessary.

*Paediatric population*
No dose adjustment is necessary (see section 4.4 and 5.1).

*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.

## 4.3 Contraindications

Hypersensitivity to azithromycin, to any other macrolide or to the excipient listed in section 6.1.

## 4.4 Special warnings and precautions for use

The eye drops solution should not be injected or be swallowed.

The eye drops solution should not be used for peri- or intra-ocular injection.

In the event of an allergic reaction, the treatment should be discontinued.

The patient should be informed that it is not necessary to continue to instil the eye drops solution after the end of treatment on the third day, even if residual signs of bacterial conjunctivitis remain.
Symptomatic relief occurs generally within 3 days. If there are no signs of improvement after 3 days, diagnosis should be reconsidered.

Contact lenses should not be worn by patients with bacterial conjunctivitis.

With the systemic use of azithromycin cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported. In ophthalmic use, this risk is not relevant since systemic exposure to the active ingredient is negligible (see section 5.2).

Paediatric population

Regarding the treatment of trachomatous conjunctivitis, comparative safety and efficacy studies have not been performed with Azyter 15 mg/g eye drops in children younger than one year, but there are no known safety concerns or differences in disease process to exclude its use in children less than one year old in this indication taking into account clinical experience in children older than one year of age in the treatment of trachomatous conjunctivitis and considering Azyter experience in children from birth in the treatment of purulent bacterial conjunctivitis.

Use in neonates

Based on the international consensus on diseases involving the eye and genital tract and susceptible to be transmitted to new-borns, non-trachomatous conjunctivitis caused by *Chlamydia trachomatis* and conjunctivitis caused by *Neisseria gonorrhoeae* require a systemic treatment.

In neonates and infants below the age of 3 months systemic infection (eg pneumonia, bacteremia) due to *Chlamydia trachomatis* may accompany conjunctivitis. In case of suspicion, systemic treatment is required.

This treatment is not intended to be used as prophylactic treatment of bacterial conjunctivitis in newborn infants.

## 4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction study has been performed with Azyter.

In view of the absence of detectable concentrations of azithromycin in the plasma during the administration of Azyter by ocular instillation (see section 5.2), none of the interactions with other medicinal products described for orally administered azithromycin is expected with use of the eye drops solution.

In the event of concomitant treatment with another eye drops solution, an interval of 15 minutes should be respected between instillation of the two solutions. Azyter should be instilled last.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

No effect on pregnancy is anticipated, since systemic exposure to azithromycin is negligible. AZYTER can be used during pregnancy.

Breastfeeding

Limited data indicate that azithromycin is excreted in breast milk, but, considering the low dose and the low systemic availability, the doses taken by the new-born are negligible. Consequently, breast feeding is possible during the treatment.

Fertility

Animal data do not suggest an effect of the treatment of azithromycin on male and female fertility. Human data are lacking. However, no effect on fertility is anticipated, since systemic exposure to azithromycin is negligible.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Vision may be transiently blurred after instillation. In this case, the patient should be advised to avoid driving or using machines until normal vision has been re-established.

## 4.8 Undesirable effects

During clinical trials and according to post-marketing safety data on Azyter eye drops solution, the following treatment-related signs and symptoms were reported:

Immune system disorders

Uncommon (≥1/1000, <1/100)
Angioedema*, hypersensitivity.

Eye disorders

Very common (≥1/10)
Ocular discomfort (pruritus, burning, stinging) upon instillation.

Common (≥1/100, <1/10)
Blurred vision, sticky eye sensation, foreign body sensation upon instillation.

Uncommon (≥1/1000, <1/100)
Conjunctivitis*, allergic conjunctivitis*, keratitis*, eczema eyelids*, eyelid oedema*, eye allergy*, conjunctival hyperemia, lacrimation increased upon instillation, erythema of the eyelid.

* adverse event has not been observed during clinical studies with Azyter. Inclusion of adverse event is based on post-marketing data. The frequency has been assigned based on 3/X, with X representing the total sample size summed up across all relevant clinical trials and studies, which is 3/879 resulting in “uncommon”.

*Paediatric population*
In paediatric clinical trials, the safety profile was similar to that in adults and no new adverse events were identified. The safety profiles in the different paediatric subsets were also similar (see Section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard

### 4.9 Overdose

The total amount of azithromycin in a single-dose container, containing a sufficient quantity for treating both eyes, is too small to induce adverse effects after inadvertent intravenous or oral administration.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibiotics, ATC code: S01AA26

Mode of action

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.

Mechanism of resistance

Generally, the resistance of different bacterial species to macrolides has been reported to occur by three mechanisms associated with target site alteration, antibiotic modification, or altered antibiotic transport (efflux). Various efflux pump systems have been described in bacteria. An important efflux system in streptococci is conferred by the *mef* genes and results in a macrolide-restricted resistance (M phenotype). Target modification is controlled by *erm* encoded methylases ($MLS_B$ phenotype) and results in cross-resistance to several classes of antibiotics (see below).

A complete cross-resistance exists among erythromycin, azithromycin, other macrolides and lincosamides and streptogramin B for *Streptococcus pneumoniae*, beta-haemolytic streptococci of group A, *Enterococcus spp.* and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA).

Constitutive mutants in inducibly resistant strains with *erm*(A) or *erm*(C) can be selected *in vitro* at low frequencies ~$10^{-7}$ cfu in the presence of azithromycin.

*Breakpoints*

The list of micro-organisms presented hereafter has been targeted to the indications (see section 4.1.).

Note that the breakpoints and *in-vitro* activity spectrum presented hereafter are those applicable to systemic use. These breakpoints may not be applicable to topical ocular application of the drug product due to the local concentrations that are reached and the local physicochemical conditions that may influence the overall activity of the agent at the site of application.

According to the EUCAST (European Committee on Antimicrobial Susceptibility Testing) the following breakpoints have been defined for azithromycin:

- *Haemophilus influenzae* : S ≤ 0.12 mg/l and R > 4 mg/l
- *Moraxella catarrhalis*: S ≤ 0.5 mg/l and R > 0.5 mg/l
- *Neisseria gonorrhoeae*: S ≤ 0.25 mg/l and R > 0.5 mg/l
- *Staphylococcus spp**: S ≤ 1.0 mg/l and R > 2.0 mg/l
- *Streptococcus pneumoniae*: S ≤ 0.25 mg/l and R > 0.5 mg/l
- *Streptococcus A, B, C, G*: S ≤ 0. 25 mg/l and R > 0.5 mg/l

**spp includes all the species of the genus*

For other species, EUCAST allows that erythromycin can be used to determine the susceptibility of the listed bacteria to azithromycin.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence is such that the utility of the agent in at least some types of infections is questionable.

**Table: Antibacterial spectrum of azithromycin for bacterial species relevant to the indications**

| **Commonly susceptible species** |
|---|
| **Aerobic Gram-negative** |
| ***Moraxella (Branhamella) catarrhalis*** |
| ***Neisseria gonorrhoeae*[1]** |
| ***Haemophilus influenzae*[$]** |
| ***Haemophilus parainfluenzae*[$]** |
| **Other micro-organisms** |
| ***Chlamydia trachomatis**** |
| **Species for which acquired resistance may be a problem** |
| **Aerobic Gram-positive** |
| ***Staphylococcus aureus* (methicillin resistant and methicillin susceptible)** |
| ***Staphylococcus*, coagulase negative (methicillin resistant and methicillin susceptible)** |
| ***Streptococcus pneumoniae*** |

| |
|---|
| ***Streptococcus pyogenes*** |
| ***Streptococci viridans*** |
| ***Streptococcus agalactiae*** |
| ***Streptococcus* group G** |
| **Inherently resistant organisms** |
| **Aerobic Gram positive** |
| ***Corynebacterium* spp.** |
| ***Enterococcus faecium*** |
| **Aerobic Gram-negative** |
| ***Pseudomonas aeruginosa*** |
| ***Acinetobacter*** |
| ***Enterobacteriaceae*** |

* Clinical effectiveness is demonstrated by sensitive isolated organisms for approved indications.

$ Natural intermediate susceptibility.

1 Conjunctivitis caused by *Neisseria gonorrhoeae* require a systemic treatment (see section 4.4).

*Information from clinical trials*

- Trachomatous conjunctivitis caused by *Chlamydia trachomatis*.

  Azyter was evaluated in a two-month, randomised, double-masked study comparing Azyter with a single oral dose of azithromycin for the treatment of trachoma in 670 children (1-10 years). The primary efficacy variable was the clinical cure at Day 60, *i.e.* a grade TF0 (simplified WHO grading scale). At Day 60, clinical cure rate of Azyter instilled twice daily for 3 days (96.3%) was non-inferior to that of oral azithromycin (96.6%).

  The clinical efficacy of Azyter (instilled twice daily for 3 days) in mass curative and prophylactic treatment of trachoma in an entire population (from birth) in a northern Cameroon district (112 000 subjects) was assessed in a multicentre, open-label, single-arm, phase IV study. Three annual treatment periods were performed. The primary efficacy endpoint was the prevalence of active trachoma, i.e. trachomatous inflammation-follicular or trachomatous inflammation-intense (TF+TI0 or TF+TI+). For analysis, clinical assessment of trachoma was performed each year in a sample of 2400 children aged ≥1 and < 10 years old selected using a random cluster sampling. The prevalence of active trachoma (TF+TI0 or TF+TI+) was 31.1% at Year 0 (before Azyter instillations) and decreased to 6.3% at Year 1, 3.1% at Year 2 and 3.1% at Year 3.
  In the whole population, there was no serious adverse event in relation with the study drug.

- Purulent bacterial conjunctivitis.

Azyter was evaluated in a randomised, investigator-masked study comparing Azyter, instilled twice daily for 3 days, with tobramycin 0.3% eye drops, instilled every two hours for 2 days then four times daily for 5 days, for the treatment of purulent bacterial conjunctivitis in 1043 patients (ITT set), including 109 children up to the age of 11 years from whom 5 were newborn infants (0 to 27 days) and 38 infants and toddlers (28 days to 23 months of age). In the Per Protocol set (n=471), there were no newborns and only 16 infants and toddlers. The clinical study was performed in different areas in Europe, North Africa, and India. The primary efficacy variable was the clinical cure at Day 9 in the PP set, defined as a score of 0 for both the bulbar conjunctival injection and the purulent discharge. At Day 9, clinical cure rate of Azyter (87.8%) was non-inferior to that of tobramycin (89.4%). Microbiological resolution rate of Azyter was comparable to that of tobramycin.

*Paediatric population*
The efficacy and safety of Azyter in paediatric patients ≤ 18 years of age was demonstrated in a randomised, investigator-masked study compared with tobramycin in 282 analysed patients diagnosed with purulent bacterial conjunctivitis (including 148 patients in the subgroup 0 day - < 24 months). Patients received either Azyter, instilled twice daily for 3 days or tobramycin 0.3% eye drops, instilled every two hours for 2 days then four times daily for 5 days. The primary efficacy endpoint was the clinical cure in the worse eye on D3 for patients with D0 positive bacterial cultures. Clinical cure in the worse eye on D3 was demonstrated to be significantly superior for Azyter (47%) than for tobramycin (28%). At D7, 89% of patients treated with Azyter were cured versus 78% with tobramycin. No statistical difference was found between treatment groups for the bacteriological resolution at D7.
Azyter (instilled twice daily for 3 days) was well-tolerated in all age groups in this large study in paediatric population. The events observed in paediatric subjects were a subset of those previously observed in adults; no new adverse events were identified in paediatric subjects. Furthermore, no age-related patterns of clinical concern were evident. The short duration of Azithromycin 1.5% treatment, the low number of instillations needed and the easiness of instilling drops in children were appreciated by both children and parents.

## 5.2. Pharmacokinetic properties

Azithromycin was not detected in the blood of patients with bacterial conjunctivitis after instillation of Azyter at the recommended dose (detection limit: 0.0002 µg/mL of plasma).

*Paediatric population*
Pharmacokinetic studies have only been performed in adults.

## 5.3 Preclinical safety data

In animals, azithromycin caused reversible phospholipidosis. This effect was seen after oral exposures which were about 300 times in excess of the maximum human exposure after ocular administration indicating little relevance to clinical use.

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

*Carcinogenic potential*

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

*Mutagenic potential*

There was no evidence of a potential for genetic and chromosome mutations in in vivo and in vitro test models.

*Reproductive toxicity*

No teratogenic effects were observed in embryotoxicity studies in rats after oral administration of azithromycin. In rats, azithromycin dosages of 100 and 200 mg/kg body weight/day led to mild retardations in fetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed. These effects were seen after oral administration at exposures which were about 1000 times in excess of the maximum human exposures after ocular administration. Because of the high safety margin, these findings do not point to a relevant risk for human reproduction.

*Ocular toxicity*

Ocular administration of Azyter eye drops to animals twice or three times a day during 28 days did not demonstrate any local or systemic toxic effect.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Triglycerides, medium-chain.

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

18 months

After opening of the single-dose container, the eye drops, solution should be used immediately.

Discard the opened single-dose container immediately after first use.

## 6.4 Special precautions for storage

Do not store above 25°C.

Keep the single-dose containers in the sachet in order to protect them from light.

### 6.5 Nature and contents of container

Single-dose low-density polyethylene container, each containing 0.25 g, enclosed in a sachet.

Pack-size: box of six single-dose containers.

### 6.6 Special precautions for disposal

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

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## 8 MARKETING AUTHORISATION NUMBER(S)

PL 20162/0012

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/07/2012

## 10 DATE OF REVISION OF THE TEXT

01/08/2013