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Bundesinstitut für Arzneimittel
und Medizinprodukte

Decentralised Procedure

RMS Public Assessment Report

Scientific Discussion

Moxifloxacin Alcon
Eye drops, solution
(Active Substance: Moxifloxacin)

DE/H/1588/001/DC

Applicant: Alcon Pharma GmbH

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I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the questions raised by RMS and CMS on quality, safety and efficacy, the RMS considers that the application for, Moxifloxacin Alcon, eye drops, in the treatment of

“treatment of bacterial purulent conjunctivitis, caused by moxifloxacin susceptible strains (see Section 5.1)

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

is approvable.

I. EXECUTIVE SUMMARY

I.1 Problem statement

Moxifloxacin hydrochloride was originally developed by Bayer AG, as tablet (400 mg) and intravenous (400 mg in 250 ml sodium chloride) formulations for the treatment of a variety of systemic infections. Bayer obtained approval to market moxifloxacin hydrochloride tablets and/or intravenous solution in numerous jurisdictions, including Germany and the USA. Resistance to older generation fluoroquinolones has emerged, as well as resistance to other antibacterial agents, which has led to the development of the more potent fourth generation fluoroquinolones (such as moxifloxacin). Moxifloxacin behaves differently from the earlier generations in terms of its microbiologic activity, or ability to bind the enzymes that are important for DNA replication. Moxifloxacin hydrochloride exhibits rapid bactericidal activity against both Gram-positive and Gram-negative bacterial pathogens, including staphylococci, *Streptococcus pneumoniae*, members of the *Enterobacteriaceae* family, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and anaerobes as well as some atypical mycobacteria. Moxifloxacin also has superior activity compared to the earlier second-generation quinolones against quinolone resistant strains of Gram-positive pathogens.

On the basis of its enhanced activity against *S. aureus* and *S. pneumoniae*, the Applicant considered that moxifloxacin hydrochloride would be effective for treating bacterial infections of the anterior segment of the eye. For example, bacterial conjunctivitis in children is predominantly caused by *S. aureus*, *H. influenzae* and *S. pneumoniae*. In adults, in addition to these pathogens, there is a wider diversity of Gram-positive and Gram-negative pathogens associated with bacterial conjunctivitis.

The indication of bacterial conjunctivitis was selected for the clinical development of Moxifloxacin Alcon 5 mg/ml Eye Drops, Solution as it is the most common ocular infection in children and is also common in adults. Although the condition may be self-resolving with time, treatment with topical ophthalmic antibiotics is justified, as it hastens resolution of the disease, thus limiting contagious spread of infection. It also decreases complications, discomfort and reduces the risk of progression to more serious corneal infections.

The claimed recommendation for use is one drop in the affected eye(s) 3 times a day.

I.2 About the product

Moxifloxacin is a synthetic fluoroquinolones antibiotic agent. Moxifloxacin hydrochloride is marketed worldwide (as the hydrochloride) under the brand name Avelox (in some countries also Avalox) for oral treatment. In most countries the drug is also available in parenteral form for intravenous infusion.

Moxifloxacin can be used to treat respiratory infections, including acute sinusitis, acute exacerbations of chronic bronchitis, and community-acquired pneumonia, as well as skin and skin structure infections. Moxifloxacin is also used for the treatment of complicated intra-abdominal infections, such as those seen in hospitals. Because moxifloxacin is primarily metabolized and eliminated via the hepatic route, it is not indicated for the treatment of urinary tract infections. Moxifloxacin is used as a second-line agent in tuberculosis (TB) and may potentially have benefits in reducing treatment duration from its current six month to four months.

Moxifloxacin Alcon 5 mg/ml Eye Drops (Formula C₂₁H₂₄FN₃O₄): Solution is a broad spectrum topical ocular antibiotic product containing the fourth generation quinolone, moxifloxacin hydrochloride.

I.3 General comments on the submitted dossier

The legal Basis of the application is Article 8(3) known active substance Moxifloxacin hydrochloride, eye drops, under the trade name Moxifloxacin Alcon. The originator product is VIGAMOX 5mg/ml Augentropfen (Moxifloxacinhydrochloride 5.45 mg, eye drops, solution) by Alcon Pharma GmbH, registered since 19-March-2006. The SPC is in line with that of the original product.

Moxifloxacin Eye Drops, Solution 5 mg/ml is approved in more than 50 countries with the first approval (as VIGAMOX) occurring in the United States of America on April 15, 2003. A review of the spontaneous post-marketing reports received as of November 30, 2007 confirms the safety profile of Moxifloxacin Eye Drops, Solution 5 mg/ml. Adverse events possibly associated with the use of Moxifloxacin 5 mg/ml are reported rarely. Moxifloxacin 5 mg/ml is well-tolerated and safe for use as indicated based upon a review of spontaneous post-marketing reports of adverse events. No reaction term has been reported with a frequency which could suggest a product-related problem.

Scientific Advice was given from the CPMP (September 2000, follow up May, 2001), from the US FDA (April, 2001) and from the Japanese Drug Organisation (DO) (December 2001). The applicant followed these Scientific Advices and has obtained approval for Moxifloxacin Alcon 5 mg/ml Eye Drops, Solution in more than 50 countries worldwide mainly in the indication: “for the treatment of bacterial conjunctivitis caused by susceptible strains of organisms”.

I.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

All manufacturing sites of the DCP procedure DE/H/1588/01/DC, which are responsible for the manufacture, assembly, packaging, quality control and batch release of the drug product, are situated within the Community.. For these manufacturing sites the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The Qualified Persons of the two manufacturers which are responsible for manufacture, where the active substance is used as a starting material, and which are also responsible for batch release in the EEA declare that the active substance manufacturer operates in compliance with the detailed guidelines on good manufacturing practice for starting materials.

II. SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Drug substance

The drug substance moxifloxacin hydrochloride is described in the European Pharmacopoeia. A full documentation of the active substance has been submitted in the dossier. The manufacturing process is adequately described. The active substance is adequately characterised and specified, including enantiomeric purity. The analytical procedures are described. Batch analysis results show compliance with the specification and with the Ph. Eur. monograph. The container closure systems are sufficiently described. A retest-period of two years has been established.

Drug Product

The drug product is a sterile ophthalmic solution. The eye drops contain 5.45 mg/ml moxifloxacin hydrochloride as active substance, corresponding to 5 mg moxifloxacin per millilitre solution. The drug product is presented in a multidose container. The drug product does not contain any preservatives. The choice and function of the excipients have been adequately explained. The choice of the manufacturing process is justified.

For manufacture of the drug product the excipients and the active substance are dissolved in purified water. The manufacturing process is validated.

All excipients are specified according to the respective Ph. Eur. monographs.

The release and the shelf-life specification cover appropriate parameters for this dosage form. Results of the analysis of production batches of both proposed manufacturing sites showed that the finished product meets the proposed specifications.

The container closure system consists of natural low-density polyethylene bottles and plugs as well as of white polypropylene closures.

A shelf-life of 36 months without any storage conditions is justified by the stability data.

The proposed in-use shelf-life of 28 days is sufficiently supported by stability data.

II.2 Nonclinical aspects

Pharmacology

Moxifloxacin hydrochloride is a fourth generation fluoroquinolones, characterised by an enhanced activity against Gram-positive bacteria, while retaining also good activity against Gram-negative species. The fluoroquinolones have been shown to inhibit DNA gyrase and topoisomerase IV as their primary mode of action.

Moxifloxacin hydrochloride was developed by Bayer for systemic administration for a variety of bacterial infections. Due to its *in vitro* susceptibility profile, moxifloxacin was selected by Alcon for development of a topical ocular formulation for bacterial conjunctivitis.

Based on *in vivo* efficacy studies in rabbits (keratitis rabbit model) 0.5% moxifloxacin was established as the most appropriate concentration of the eye drop solution.

The safety margin determined in all of the general pharmacology studies conducted by Bayer is considered sufficiently wide for moxifloxacin hydrochloride administered by the topical ocular route to preclude any concerns of significant systemic adverse events occurring in human beings.

Pharmacokinetics

In addition to the extensive systemic pharmacokinetic studies of moxifloxacin hydrochloride in rodents, monkeys, dogs and swine performed by Bayer, Alcon has conducted studies to determine the distribution of moxifloxacin in rabbit ocular tissues and tear film following a single ocular dose.

Furthermore, toxicokinetic data from topical ocular toxicity studies in pigmented rabbits (1 month) and monkeys (3-months) were generated.

Moxifloxacin was well absorbed into the rabbit eye and concentrations in cornea and tear film remained above the minimum inhibitory concentration for moxifloxacin susceptible organism up to 6 hours post dosing. Contrary, only low systemic exposure was noted following topical ocular application, thus a substantial margin of safety for Moxifloxacin Eye Drops, Solution 5 mg/ml can be assumed.

In animals, low secretion into mother's milk was observed after oral administration. Following topical ocular administration of Moxifloxacin Alcon in healthy subjects (3 drops daily, bilateral application, 4

days) only low moxifloxacin plasma concentrations were reported (C_{max} and AUC were 2.7 ng/ml and 41.9 ng h/ml), thus no relevant exposure of the infant is to be expected during breast-feeding.

Toxicology

A complete program of toxicity studies has been performed by Bayer to substantiate the systemic safety of moxifloxacin hydrochloride tablets. Reports from these studies have been evaluated previously by competent regulatory authorities during marketing authorisation procedure for moxifloxacin hydrochloride 400 mg tablets

Additional topical ocular toxicity studies in animals have been performed by Alcon with Moxifloxacin ophthalmic solutions at concentrations as high as 30 mg/mL, i.e. 6 times higher than the intended clinical formulation. These data reveal that the developed ophthalmic solution is well tolerated and exhibits only a low potential for ocular irritation. Whereas in all rabbit and monkey plasma samples of the three dose groups (0.5%, 1% and 3%) quantifiable level were detected, no signs of ocular or systemic toxicity were observed. Due to the more frequent dosing in monkeys, all plasma concentration samples (Day 1 and 14) exceeded the reported maximum level in humans (5.95 ng/mL) even at the lowest concentration (0.5%) by 2-to 7 times. However, AUC values measured in rabbits and monkeys indicate no significant accumulation of drug in plasma over the course of treatment (up to 3 months).

The developed 0.5% moxifloxacin ophthalmic solution is free of any added preservative such as benzalkonium chloride, and a comparable solution with 1% moxifloxacin showed no evidence of delayed dermal contact sensitisation in the guinea pig. The active principle, Moxifloxacin hydrochloride, is a novel 8-methoxy-6-fluoroquinolone, that lacks phototoxic and photomutagenic properties of older quinolones.

In summary, the results of comprehensive non-clinical toxicology testing conducted by Alcon and Bayer do not indicate any safety concern for Moxifloxacin Eye Drops, Solution 5 mg/ml at the proposed dose and duration of treatment, i.e. one drop to the affected eye, three times a day for four days.

II.3 Clinical aspects

The initial clinical development plan for Moxifloxacin Alcon 5 mg/ml Eye Drops, Solution included 10 completed trials: 3 multiple dose pharmacokinetic studies (C-01-48, C-01-16 and C-02-22), one tear concentration study (C-01-53), one skin sensitisation study (C-01-09), and 5 safety and efficacy trials. Of these 5 trials, 3 evaluated Moxifloxacin Eye Drops, Solution 5 mg/ml versus Vehicle (C-00-02, C-00-55 and C-01-66), one study compared Moxifloxacin Eye Drops, Solution 5 mg/ml to Ofloxacin Eye Drops, Solution 3 mg/ml (C-00-46), and a fifth study involved Moxifloxacin Eye Drops, Solution 5 mg/ml and Ciprofloxacin Eye Drops, Solution 3 mg/ml in paediatric patients less than one month of age (C-01-34). Additionally, a specific clinical development plan for Moxifloxacin Eye Drops, Solution 5 mg/ml was undertaken with the purpose of registration in Japan.

Pharmacokinetics

Moxifloxacin Eye Drops, Solution 5 mg/ml is applied topically directly to the site of action. Accordingly, clinical pharmacokinetic studies were not performed for the purpose of evaluating or comparing formulations. Clinical pharmacokinetic studies of moxifloxacin after oral and intravenous administration were conducted by Bayer, and which many are cited in the literature. A number of pharmacokinetic studies with moxifloxacin hydrochloride conducted by various investigators are also published. The Applicant conducted topical ocular studies to assess systemic exposure and to assess levels of drug in the tear film.

The pharmacokinetics of moxifloxacin following topical ocular administration have been studied in Japanese and Caucasian healthy male volunteers (C-01-16), and in healthy male and female Asian (Japanese) and Caucasian volunteers (C-01-48) receiving topical ocular doses (1 drop per eye) 3 times a day for 14 $\frac{1}{3}$ and 4 $\frac{1}{3}$ days, respectively.

In a separate study, the steady-state pharmacokinetics of moxifloxacin were studied in Japanese male subjects who were administered 8 times daily topical ocular doses for 14 days (C-02-22) which is the

maximum recommended regimen for the treatment of bacterial corneal ulcers in Japan. These 3 pharmacokinetic studies were conducted to assess the systemic exposure of moxifloxacin. The total daily topical dose of moxifloxacin (approximately 1140 ng based on a 190 ng per 38 all drop with bilateral one-drop dosing 3 times a day, i.e., 6 drops a day) is 350-fold lower than the therapeutic oral 400 mg tablet doses of moxifloxacin hydrochloride studied by Bayer. Based on plasma concentrations, the mean steady-state peak systemic exposure seen following 3-times-daily (2.70 ng/ml) or 8-times-daily topical administration (1.95 ng/ml) is at least 1667-fold lower than that observed following once daily oral administration (4.5 ng/ml).

Pharmacodynamic

Moxifloxacin is active against a broad spectrum of Gram positive and Gram negative ocular pathogens, atypical microorganisms and anaerobes. Moxifloxacin and other fluoroquinolones antimicrobials exert their antimicrobial activity by inhibiting bacterial DNA synthesis, a process that ultimately results in bacterial cell death. Quinolones inhibit bacterial DNA synthesis by interfering with the enzymatic activity of bacterial DNA gyrase, an enzyme catalysing a reaction that alters DNA topology. DNA gyrase creates negative superhelices that help to stabilise DNA separation and prevent excessive and undesirable coiling of the double strands during replication. In addition to DNA gyrase, another type of enzyme belonging to the same class of DNA enzymes called topoisomerases is topoisomerase type IV. By targeting both DNA gyrase and topoisomerase IV, moxifloxacin and other fluoroquinolones arrest bacterial cell growth and division by stabilising the DNA-enzyme complex, this temporarily results in bacteriostasis. Subsequently, bacteria attempt but are unable to repair the DNA lesion. DNA ends from the fluoroquinolones-gyrase-DNA complex are eventually liberated, creating lethal double-strand DNA breaks. Thereby, fluoroquinolones are bactericidal as well as bacteriostatic. Although both DNA gyrase and topoisomerase IV are targets of fluoroquinolones, the degree of targeting is organism-specific. In *Escherichia coli*, DNA gyrase is the primary and topoisomerase IV is the secondary enzymatic target. Topoisomerase IV is the primary drug target for *Staphylococcus aureus*. This difference in drug targeting has important implications with regard to the spectrum of activity and the potential for development of resistance. Moxifloxacin demonstrates excellent concentration-dependent bactericidal activity against a wide range of microorganisms including Gram-positive cocci, aerobic or intracellular bacteria, and “atypical” organisms such as *Mycoplasma*, *Mycobacterium* and *Chlamydia*. The C-8-methoxy moiety confers increased bactericidal activity against *S. aureus* and *Escherichia coli* including those strains that contain one-step mutation in topoisomerase II or IV.

Mechanism of resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may also affect susceptibility to moxifloxacin.

In vitro resistance to moxifloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Moxifloxacin is a poor substrate for active efflux mechanisms in Gram-positive organisms.

Cross-resistance is observed with other fluoroquinolones. However, as moxifloxacin inhibits both topoisomerase II and IV with similar activity in some Gram-positive bacteria, such bacteria may be resistant to other quinolones, but susceptible to moxifloxacin.

Susceptibility to Moxifloxacin:

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.

Clinical efficacy

Three clinical randomized double-blind study to demonstrate superiority to vehicle and three clinical randomized double-blind study to demonstrate therapeutically equivalence were conducted with patients in the proposed indication “bacterial conjunctivitis”.

In these studies therapeutically equivalence of the test drug with well known current established and marked therapeutically regimes (OCUFLOX, CILOXAN and Levofloxacin) was confirmed. In four randomised, double masked, multicentre, controlled clinical trials in which patients were dosed 3 times a day for 4 days, Moxifloxacin Alcon produced clinical cures in 80% to 94% of patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of the baseline pathogens ranged from 78% to 97%. Efficacy of the medicinal product in the topical treatment of other bacterial infections of the anterior segment of the eye, caused by moxifloxacin susceptible strains, than bacterial conjunctivitis is only shown in open uncontrolled studies.

Clinical safety

The 5 completed safety and efficacy trials included originally in this submission (C-00-02, C-00-55, C-01-66, C-00-46 and C-01-34) involved a total of 993 patients exposed to Moxifloxacin Eye Drops, Solution 5 mg/ml in USA and India. Additionally, there were 584 patients exposed to Moxifloxacin Eye Drops, Solution 5 mg/ml in 4 clinical efficacy and safety studies (C-01-93, C-02-24, C-02-25 and C-02-26) conducted in Japan. Across all studies, the patients ranged in age from 2 days to 96 years.

The applicant present data about over 1700 patients in clinical studies. Moxifloxacin Alcon was administered up to 8 times a day, with over 1450 of these patients receiving treatment 3 times daily. No serious ophthalmic or systemic undesirable effects related to Moxifloxacin Alcon were reported in any of the clinical studies. The most frequently reported treatment-related undesirable effects with Moxifloxacin Alcon were eye irritation and eye pain, occurring at an overall incidence of 1 to 2%. These events were mild in 97% of those patients who experienced them, with only 1 patient discontinuing therapy as a result.

Paediatric patient:

In paediatric patients, Moxifloxacin Alcon produced safety and efficacy (clinical cure in 80% of patients with bacterial conjunctivitis). Clinical cure rates in patient populations including neonates, infants and toddlers, children, adolescents and adults of all ages were similar to the overall study results. Also in very young children the microbiological success rate for the eradication of the baseline pathogens was 92% in patients from birth up to one month.

Adverse events:

No untoward safety issues were identified in patients administered Moxifloxacin 5 mg/ml three-times-daily based upon a review of adverse events, which included an assessment of incidence, seriousness (serious/non-serious), treatment-relatedness, rate of patient discontinuation due to adverse events, and individual adverse event characteristics (e.g., severity, onset, duration).

Special groups:

The diversity of ethnic groups included in the clinical studies is reflective of that found across Europe, and the environmental conditions across the USA and India are similar to those in Europe. The presented data are sufficient. The outcomes for clinical cure and microbiological eradication of the baseline pathogen at the test-of-cure visit, by age, gender and race, were similar to the outcomes for the overall population studied.

Overall conclusion:

The data provides sufficient evidence of the safety and efficacy (shorter duration than vehicle, non-inferiority to established therapy) of Moxifloxacin Eye Drops, Solution 5 mg/ml for the treatment of “bacterial purulent conjunctivitis, caused by moxifloxacin susceptible strains.

Pharmacovigilance system

Alcon provided the description of the Pharmacovigilance system.

Risk Management Plan

Based on published literature and to Alcon's pre and post market experience, moxifloxacin is generally well tolerated. Data from meta-analysis of phase II and III trials involving approximately 4,900 patients indicate that most adverse effects were mild and transient. Moxifloxacin had similar rates of adverse events as comparator agents (ciprofloxacin, ofloxacin, levofloxacin). However, a potential for serious systemic effects and identified ocular effects exists. The following potential and identified risks were identified:

- Corneal disorders (identified)
- Hypersensitivity reactions (identified)
- Musculoskeletal and connective tissue disorders (potential)
- QT-interval prolongation (potential)

- potential for off-label use

Corneal disorders:

Formation of a white crystalline deposit or precipitate on the corneal surface, occurs in up to 17.6% of human eyes treated with fluoroquinolones. This occurs more commonly with ciprofloxacin than with norfloxacin, and occurs irrespective of formulation (ophthalmic solution or ointment). From the applicants point of view this risk does not require any additional action.

Compared with all other adverse reactions the number of corneal effects is high. The adverse event profile of Moxifloxacin 5 mg/ml Eye Drops, Solution in patients with concurrent corneal diseases/disorders is limited at this time because Patients with any ocular disease or disorder were excluded.

Overall the corneal effects of Moxifloxacin 5 mg/ml Eye Drops need special attention. The applicant should closely monitor all cases of corneal disorders and corneal reactions should be reviewed in the first PSURs.

Hypersensitivity reactions:

A review of all the cases possibly involving allergic or hypersensitivity reactions shows that most reactions involved non-serious ocular events that resolved shortly after product discontinuation.

The potential for serious hypersensitivity reactions to Moxifloxacin Alcon 5 mg/ml Eye Drops does not represent a significant safety concern.

Musculoskeletal and connective tissue disorders

Systemic application of fluoroquinolones has the potential to damage tendons. There is no information on the incidence or prevalence of musculoskeletal disorders associated with the use of topical ocular fluoroquinolones.

It is currently unclear as to whether topical dosing with moxifloxacin can cause musculoskeletal and connective tissue adverse reactions. However, one case was reported. The applicant should monitor all cases closely.

QT-interval prolongation

It seems that the risk of QT-interval prolongation is negligible after ocular moxifloxacin exposure. No particular measures are required.

Potential for off-label use

During the post-marketing phase Moxifloxacin Alcon 5 mg/ml Eye Drops has been used mainly according to the approved indication. There have been some reports of Moxifloxacin 5 mg/ml Eye Drops being used intracamerally for the prophylaxis of endophthalmitis following intraocular surgery.

The off-label use of Moxifloxacin 5 mg/ml Eye Drops should be monitored closely via routine pharmacovigilance practices, including review of the literature and post-marketing spontaneous reports.

Overall, the applicant has no additional pharmacovigilance activities planned at this time date. Based on the information that has been collected both spontaneously and from clinical trials, there is no evidence to support the need for specific pharmacovigilance actions. No pharmacovigilance studies or targeted post-marketing studies are planned.

Routine pharmacovigilance activities are considered to be sufficient. Additionally the above mentioned close monitoring and reviews should be realised.

III. BENEFIT RISK ASSESSMENT

The application contains an adequate review of published clinical data about products with similar formulations. The benefit-risk-relation is positive:

1. The optimal dose ranges and dosage regimens are not investigated. However, the proposed posology is sufficient and well tolerated.
2. No differences in efficacy and safety in subpopulations (e.g. as defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphism) is proven.
3. Local medicinal product interaction studies have not been conducted. Interactions with other used local medicinal product are possible. Therefore, the simultaneous use with other medicinal products is not recommended. If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart to avoid possible interaction effects.
4. Based on published literature and to Alcon's pre- and post-market experience, moxifloxacin is generally well tolerated. However, some potential risks were identified. Routine pharmacovigilance activities are considered to be sufficient. Additionally, the applicant should closely monitor all cases of corneal disorders, musculoskeletal/connective tissue disorders and off-label use. Corneal reactions should be reviewed in the first PSURs.
5. In paediatric patients, Moxifloxacin Alcon produced safety and efficacy (clinical cure in 80% of patients with bacterial conjunctivitis).

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for, Moxifloxacin Alcon, eye drops, in the treatment of

“treatment of bacterial purulent conjunctivitis, caused by moxifloxacin susceptible strains (see Section 5.1)

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

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