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<td>May 21, 2010</td>
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<td>November 19, 2010</td>
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<td>Division / Office</td>
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<tr>
<td>Reviewer Name(s)</td>
<td>Lucious Lim, M.D., M.P.H.</td>
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<td>Review Completion Date</td>
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<tr>
<td>Established Name</td>
<td>moxifloxacin hydrochloride ophthalmic solution 0.5% as base</td>
</tr>
<tr>
<td>(Proposed) Trade Name</td>
<td>Moxeza</td>
</tr>
<tr>
<td>Therapeutic Class</td>
<td>quinolone</td>
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<td>Alcon Research Ltd.</td>
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<td>Formulation(s)</td>
<td>Ophthalmic solution</td>
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<tr>
<td>Dosing Regimen</td>
<td>One (1) drop in the affected eye(s) twice a day</td>
</tr>
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<td>Indication(s)</td>
<td>Bacterial conjunctivitis</td>
</tr>
<tr>
<td>Intended Population(s)</td>
<td>Patients ages 1 year and older with bacterial conjunctivitis</td>
</tr>
</tbody>
</table>
Clinical Review
Lucious Lim, M.D., M.P.H.
NDA 22-428
Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that NDA 22-428 be approved with the labeling revisions found in this review.

1.2 Risk Benefit Assessment

The data contained in the clinical trial submitted in this re-submission (Study C-07-40) along with the Agency’s prior finding of efficacy of moxifloxacin hydrochloride ophthalmic solution 0.5% in NDA 21-598 (Vigamox) establish the efficacy of moxifloxacin AF in the treatment of bacterial conjunctivitis. Study C-07-40 met its pre-specified primary endpoint of clinical cure at Day 4. Microbiological success was also demonstrated at Day 4.

There are no new safety concerns raised in this NDA submission concerning the use of moxifloxacin for the treatment of bacterial conjunctivitis. The adverse events reported during the phase 3 studies were similar to those listed in the package insert of the currently marketed fluoroquinolone ophthalmic solutions. No clinically significant differences were found between moxifloxacin AF and the active control Vigamox in the frequency or type of adverse events.

The benefit of moxifloxacin in the treatment of bacterial conjunctivitis has been demonstrated in this NDA application. The risk for using this drug is minimal and is consistent with the currently marketed Vigamox.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommended postmarket risk evaluations and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended postmarket clinical study requirements and commitments.

2 Introduction and Regulatory Background

Moxifloxacin is a fourth generation quinolone that was originally developed and approved for the treatment of various systemic bacterial infections. Alcon developed a topical ophthalmic formulation of moxifloxacin marketed as Vigamox for the treatment of bacterial conjunctivitis. The approved dosage and administration for Vigamox is one drop in the affected eye 3 times a
day for 7 days. The current application is for an alternate formulation of moxifloxacin for the treatment of bacterial conjunctivitis. The alternate formulation contains a xanthan gum [b] [4] which is expected by Alcon to increase corneal retention time. The objective of this change is to maintain the same efficacy as Vigamox with only twice a day dosing.

2.1 Product Information

Established Name: moxifloxacin hydrochloride ophthalmic solution 0.5%
Proposed Trade Name: Moxeza
Chemical Class: new formulation
Pharmacological Class: quinolone
Indication: treatment of bacterial conjunctivitis

Dosing Regimen: One drop in the affected eye(s) two times a day for seven days
Age Groups: adults and children over the age of four months

2.2 Tables of Currently Available Treatments for Proposed Indications

Ophthalmic products currently approved for the treatment of bacterial conjunctivitis include azithromycin ophthalmic solution, tobramycin ophthalmic solution, gentamicin ophthalmic solution, erythromycin ophthalmic ointment, ciprofloxacin ophthalmic solution, ofloxacin ophthalmic solution, levofloxacin ophthalmic solution, norfloxacin ophthalmic solution, gatifloxacin ophthalmic solution, and moxifloxacin ophthalmic solution.

2.3 Availability of Proposed Active Ingredient in the United States

Moxifloxacin hydrochloride was approved in Alcon’s NDA 21-598 for Vigamox and is currently being marketed in the United States. Moxifloxacin hydrochloride is manufactured by Bayer AG in Wuppertal, Germany.

2.4 Important Safety Issues With Consideration to Related Drugs

Ophthalmic anti-infectives are generally well tolerated and effective for bacterial conjunctivitis. There are no specific issues which warrant special attention.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Alcon’s proposed phase 3 development program for moxifloxacin AF ophthalmic solution was discussed with the Agency in a pre-IND/end of phase 2 meeting on March 3, 2005. Alcon subsequently submitted Special Protocol Assessment requests for study C-04-38 and C-04-40, to which the Agency responded with comments on June 22, 2005. Comments on both studies were provided to the applicant. A pre-NDA meeting package containing a summary of efficacy
results from these studies was submitted to the Agency and comments were discussed at the pre-NDA meeting on April 8, 2008.

2.6 Other Relevant Background Information

The original NDA submission was submitted on December 12, 2008. FDA issued a complete response letter dated October 7, 2009, stating that there was a lack of substantial evidence to demonstrate efficacy in the submission. The Agency recommended that any resubmission contain the results from at least one additional vehicle-controlled clinical trial.

Moxifloxacin AF is not marketed in any other country.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was of sufficient quality to allow for a substantive review without requiring additional clinical information requests for the sponsor.

3.2 Compliance with Good Clinical Practices

The clinical studies included in this application conformed with Good Clinical Practices.

3.3 Financial Disclosures

Alcon has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for moxifloxacin AF ophthalmic solution. There are three investigators who participated in the phase (b)(6) who have disclosed financial ties to the sponsor.

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>Investigators</th>
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</thead>
<tbody>
<tr>
<td>(b)(6)</td>
<td></td>
</tr>
</tbody>
</table>

Reviewer’s Comments:

A review of these arrangements does not raise questions about the integrity of the data.
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Moxifloxacin Alternative Formulation Ophthalmic solution, 0.5% is a sterile, stable, self-preserved ophthalmic solution containing 0.545% w/v moxifloxacin hydrochloride. The product was developed using the same active ingredient and for the same indication (topical treatment of bacterial conjunctivitis) as Vigamox. The modified formulation contains a xanthan gum.

Composition of Moxifloxacin AF Ophthalmic Solution

<table>
<thead>
<tr>
<th>Component</th>
<th>Percent w/v</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin hydrochloride</td>
<td>0.545</td>
<td>Active</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>(b) (4)</td>
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<tr>
<td>Sodium chloride</td>
<td>(b) (4)</td>
<td></td>
</tr>
<tr>
<td>Boric acid</td>
<td>(b) (4)</td>
<td></td>
</tr>
<tr>
<td>Sorbitol</td>
<td>(b) (4)</td>
<td></td>
</tr>
<tr>
<td>Tyloxapol</td>
<td>(b) (4)</td>
<td></td>
</tr>
<tr>
<td>Hydrochloric acid and/or sodium hydroxide</td>
<td>Adjust pH to 7.4</td>
<td>Adjust to pH 7.4</td>
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<td>Purified water</td>
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</table>

Comparison of Compositions of Moxifloxacin AF and Vigamox

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<thead>
<tr>
<th>Component</th>
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<tr>
<td>Xanthan gum</td>
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<td>Tyloxapol</td>
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<td>Hydrochloric acid and/or sodium hydroxide</td>
<td>Adjust pH to 7.4</td>
</tr>
<tr>
<td>Purified water</td>
<td>(b) (4)</td>
</tr>
</tbody>
</table>
The formulation of Moxifloxacin AF that was used in the clinical studies are the same as the one intended for marketing.

4.2 Clinical Microbiology

See section 6.1.10.

4.3 Preclinical Pharmacology/Toxicology

Ocular PK studies in rabbits showed that the concentration of moxifloxacin in tears fell more rapidly following application of Vigamox than following application of Moxifloxacin AF. Additionally, the levels of moxifloxacin in the aqueous humor of rabbits were higher after application of Moxifloxacin AF compared to Vigamox. Although the clinical significance is not known.

Moxifloxacin AF was well tolerated by rabbits when applied to the eyes several times daily for one month. Neither ocular irritation nor toxicity was observed with the formulation and concentration of active ingredient to be marketed. There were microscopic signs of slight irritation at higher moxifloxacin concentrations >1% (same vehicle as Moxifloxacin AF), but no inflammation.

Moxifloxacin AF appears reasonably safe to use as directed. This product caused neither ocular irritation nor toxicity when applied to rabbit eyes several times daily for one month.

See Pharm/Tox review for additional findings.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action for moxifloxacin was previously submitted and evaluated as part of the Vigamox NDA (NDA 21-598). The antibacterial action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division.

4.4.2 Pharmacodynamics

See Biopharmaceutics review.
4.4.3 Pharmacokinetics

See Biopharmaceutics review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Study Design</th>
<th>Subject/Patient Population</th>
<th>Treatment Groups</th>
<th>Dosing Regimen</th>
<th>Dosing duration</th>
<th>Total No. Subjects/Patients Enrolled</th>
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</thead>
</table>
| C-07-40 Safety/efficacy study | Prospective, multi-center randomized, vehicle-controlled, double-masked | Patients 1 month of age and older with bacterial conjunctivitis | Moxifloxacin AF ophthalmic solution  
Vehicle          | 1 drop BID OU                                   | 3 days                                                         | 1179 (847 culture positive diagnosed eye) |

5.2 Review Strategy

This re-submission contained one additional safety and efficacy trial to support the approval of moxifloxacin AF for the treatment of bacterial conjunctivitis. Study C-07-40 was a two-arm superiority trial comparing moxifloxacin AF to vehicle.

The original NDA submission contained two safety and efficacy trials to support the approval of moxifloxacin AF for the treatment of bacterial conjunctivitis. Study C-04-38 was a two-arm superiority trial comparing moxifloxacin to vehicle; study C-04-40 was a non-inferiority trial which compared the new formulation to the currently marketed Vigamox. Study C-04-38 failed its pre-specified primary efficacy endpoint of clinical cure at day 7; however, microbiological eradication was demonstrated at this timepoint. Since a non-inferiority margin has not been established for Vigamox, Study C-04-40 was not viewed as a study that could be used to establish the efficacy moxifloxacin AF and was considered supportive evidence.

All three studies were used in the safety analysis.

5.3 Discussion of Individual Studies/Clinical Trials
Study C-07-40

Title: An Evaluation of the Safety and Efficacy of Moxifloxacin AF Ophthalmic Solution 0.5% for the Treatment of Bacterial Conjunctivitis in the USA

Study Design

This study was a prospective, multi-center (32 sites), double-masked, parallel group, randomized, placebo-controlled trial designed to evaluate the efficacy and safety of topical ocular moxifloxacin AF ophthalmic solution compared to vehicle in the treatment of bacterial conjunctivitis in patients one month of age or older. Approximately 1644 patients with a clinical diagnosis of bacterial conjunctivitis were targeted for enrollment to achieve at least 822 (411 on moxifloxacin AF ophthalmic solution and 411 on vehicle) bacterial pathogen positive patients. Enrollment in the study included patients one month of age or older and excluded all considerations of race, occupation, socioeconomic status, or gender.

On Day 1, eligible patients who met all inclusion/exclusion criteria were randomized into one of two treatment groups, moxifloxacin AF ophthalmic solution or vehicle. Both groups were dosed with one drop two times per day. Treatment continued for 3 days with a test-of-cure (clinical) follow-up visit at 12 to 48 hours after the last dose of study medication [Day 4, End of Therapy (EOT)].
<table>
<thead>
<tr>
<th>Procedures</th>
<th>Day 1 (Screening/ Baseline) Visit</th>
<th>Day 3 (-1) Visit</th>
<th>Day 4(EOT)/Exit Visit&lt;sup&gt;a&lt;/sup&gt; Or Early Exit Visit&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>Changes in concomitant medication or general health</td>
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<td>X</td>
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<tr>
<td>Patients or Parent/Guardian Rate Ocular Symptoms</td>
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<td>X</td>
<td>X</td>
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<td>Visual Acuity LogMAR</td>
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<tr>
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<td>X&lt;sup&gt;h&lt;/sup&gt;</td>
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</tr>
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</tr>
<tr>
<td>Complete Exit Form</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>a</sup> The Day 4 (EOT)/Exit Visit was conducted 12 to 48 hours after the last study dose and was performed by an ophthalmologist sub-investigator at sites where the principal investigator was a non-ophthalmologist.

<sup>b</sup> If a patient exited prior to the Day 4 (EOT)/Exit Visit, an Early Exit Visit was conducted that included all Day 4 procedures. This exam was performed within 24 hours of exit by an ophthalmologist Sub-Investigator at sites where the principal investigator was a non-ophthalmologist.

<sup>c</sup> Assent collected for patients over 6 and under 18 years of age, if applicable.

<sup>d</sup> For women of child-bearing potential. UPT done before instillation of drug and at study exit.

<sup>e</sup> Specimens were collected prior to the fundus exam.

<sup>f</sup> All Day 1 (Screening/Baseline) Visit and Day 4 fundus examinations by Ophthalmologist utilized pupil dilation. All Day 1 (Screening/Baseline) Visit non-ophthalmologist fundus exams were undilated. A red reflex fundus exam was conducted in infants and uncooperative children.

<sup>g</sup> After dosing

<sup>h</sup> As needed
Inclusion Criteria

1. One month of age or older, of any race and either sex
2. Diagnosed with bacterial conjunctivitis in 1 or both eyes based upon the following clinical observations:
   • A rating of $\geq 1$ for bulbar conjunctival injection and
   • A rating of $\geq 1$ for conjunctival discharge/exudate in at least 1 eye (the same eye) at the Day 1 (Screening/Baseline) Visit, and
   Note: Rating was on a scale of 0-3 (absent to severe)
   • Must have been experiencing matting, currently or upon waking.
3. Were able to understand and sign an informed consent form that was approved by an Institutional Review Board/Independent Ethics Committee (IRB/IEC). If the patient was under 18 years of age, the informed consent must have been understood and signed by the patient’s legally authorized representative (parent or guardian). Assent to participate in the study was obtained from patients over 6 and under 18 years of age unless not allowed by local regulation.
4. Agreed to comply with the visit schedule and other requirements of the study. The parent or guardian must have agreed to ensure compliance of patients less than 18 years of age.
5. Women who were not pregnant and not lactating. Women who were post-menopausal or surgically sterilized. All women of childbearing potential (those who were post-menarcheal, pre-menopausal and not surgically sterile) could participate only if they had a negative urine pregnancy test prior to randomization, and if they had agreed to use adequate birth control methods to prevent pregnancy throughout the study. Adequate birth control methods included hormonal, topical, oral, implanted or injected contraceptives; mechanical – spermicide in conjunction with a barrier such as a condom or diaphragm, intrauterine device (IUD); surgical sterilization of partner.

Exclusion Criteria

1. Signs and symptoms of bacterial conjunctivitis for longer than 4 days prior to Day 1 (Screening/Baseline) Visit
2. Abnormal findings in the posterior pole of the retina or any media opacity found in a fundus examination at the Day 1 (Screening/Baseline) Visit
3. Presence of inflammation and/or active structural change in the cornea, iris, anterior chamber or lens at the Day 1 (Screening/Baseline) Visit
4. Presence of corneal opacity or any corneal abnormality at the Day 1 (Screening/Baseline) Visit that would impact the outcome of the study
5. Presence of concomitant viral infection
6. Presence of nasolacrimal duct obstruction at Day 1 (Screening/Baseline) Visit
7. Infants who had suspected or confirmed ophthalmia neonatorum of gonococcal, Chlamydia, herpetic or chemical origin
8. Infants whose birth mothers had any sexually transmitted disease within 1 month prior to delivery
9. Infants who were undergoing treatment for retinopathy of prematurity
10. Contact lens wear during the course of the study
11. Patients who had only 1 sighted eye or vision in either eye not correctable to 0.6 logMAR units (20/80) or better (using ETDRS chart). For patients who were too young to use an ETDRS chart, an age appropriate measurement method supplied by the Sponsor in accordance with the American Academy of Pediatrics Eye Examination and Vision Screening in Infants, Children and Young Adults (RE9625) Policy Statement was used. The policy statement stated that formal vision screening should begin at 3 years of age. Visual acuity measurements for children under 3 were done at the discretion of the Investigator. If not conducted, the child had to be able to fixate on and follow a moving object. Visual acuity was measured using the same method for each patient at each visit.
12. Suspected fungal, viral (e.g., Herpes Simplex) or Acanthamoeba infection, based upon clinical observation
13. Use of any preserved topical ocular medications (prescribed or OTC) at the time of entry into the study or during study participation
14. Use of any oral or topical ocular antibacterial agent within the 72 hours prior to Day 1 (Screening/Baseline) Visit or during study participation
15. Use of systemic steroids within 14 days prior to Day 1 (Screening/Baseline) Visit. Use of topical ocular steroids or non-steroidal anti-inflammatories (NSAIDs) within 1 week prior to Day 1 (Screening/Baseline) Visit. Use of these medications was not allowed during study participation. Use of nasal inhaled steroids was not allowed during the study. Bronchial steroids by inhaler were allowed; however, nebulized steroids were excluded. Topical dermal steroids were allowed except on the face.
16. Use of systemic non-steroidal ant-inflammatory (NSAIDs) within 24 hours prior to Day 1 (Screening/Baseline) Visit or any time during the study unless the patient had been on a steady (not as needed) treatment regimen for at least 2 months prior to entry and the therapy was continued throughout the study. Acetaminophen (e.g., Tylenol) PRN was allowed.
17. Any systemic or ocular disease or disorder, complicating factors or structural abnormality that would have negatively affected the conduct or outcome of the study (e.g., hepatitis, acute or chronic renal insufficiency or corneal anesthesia) or have represented in the opinion of the Investigator an undue risk to the patient.
18. Any immunosuppressive disorder (e.g., HIV-positive), or use of immunosuppressive therapy (including chemotherapy)
19. Known or suspected allergy or hypersensitivity to fluoroquinolones
20. Pregnant or lactating women, women who had a positive urine pregnancy test, or women of childbearing potential who were not using adequate birth control to prevent pregnancy
21. Participation in any other investigational clinical study within 30 days prior to study entry
22. Any patient who had a family member currently enrolled in this study
23. Any patient who was on staff at the investigational site or was a family member of staff personnel.

Additionally, the Medical Monitor could have declared any patient ineligible for a sound medical reason.
Clinical Review
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Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

Primary Efficacy Variable(s)

The primary efficacy variable was clinical cure at the Day 4 [EOT/Exit Visit (12-48 hours after the last dose)]. Clinical cure was attained if the sum of the 2 cardinal ocular signs of bacterial conjunctivitis (bulbar conjunctival injection and conjunctival discharge/exudate) was zero (i.e., normal or absent) at Day 4. The primary microbiological efficacy variable was the bacterial eradication rate at Day 4 [EOT/Exit Visit (12-48 hours after the last dose)].

Secondary Efficacy Variable(s)

The secondary efficacy variables were the eight individual signs and symptoms of bacterial conjunctivitis (bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia) at Day 3 and Day 4 (EOT)/Exit Visits and sustained clinical cure at the Day 3 Visit. A cure for an individual ocular sign or symptom was attained if the score was zero (i.e., absent or normal) and remained zero (for Day 3 findings) throughout the rest of the study. Likewise, sustained clinical cure at the Day 3 Visit was attained if the score was zero (i.e., absent or normal) and remained zero throughout the rest of the study.

Primary Efficacy Analysis

The primary statistical objective of the study was to demonstrate that Moxifloxacin AF Ophthalmic Solution was superior to Moxifloxacin AF Vehicle in the treatment of bacterial conjunctivitis. Primary efficacy had two components, clinical and microbiological.

Investigators

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Clinical Review  
Lucious Lim, M.D., M.P.H.  
NDA 22-428  
Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

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Clinical Review  
Lucious Lim, M.D., M.P.H.  
NDA 22-428  
Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

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6 Review of Efficacy

Efficacy Summary

6.1 Indication

Treatment of bacterial conjunctivitis in patients ≥ 1 year of age.
6.1.1 Methods

Description of the clinical trial design is contained in Section 5.3.

6.1.2 Demographics

**Patient Demographics**

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<td>8</td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>American Indian</td>
<td>6</td>
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<tr>
<td>Other</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Multi-Racial</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 days to 23 months</td>
<td>49</td>
<td>47</td>
</tr>
<tr>
<td>2 to 11 years</td>
<td>174</td>
<td>184</td>
</tr>
<tr>
<td>12 to 17 years</td>
<td>71</td>
<td>72</td>
</tr>
<tr>
<td>18 to 64 years</td>
<td>257</td>
<td>230</td>
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<tr>
<td>≥ 65 years</td>
<td>42</td>
<td>53</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
<td>240</td>
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<tr>
<td>Female</td>
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<td>338</td>
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<td><strong>Iris color</strong></td>
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<tr>
<td>Brown</td>
<td>331</td>
<td>315</td>
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<td>Blue</td>
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<td>Hazel</td>
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<td>Green</td>
<td>38</td>
<td>44</td>
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<td>Grey</td>
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<td><strong>Culture positive</strong></td>
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<tr>
<td>Yes</td>
<td>424</td>
<td>423</td>
</tr>
<tr>
<td>No</td>
<td>169</td>
<td>163</td>
</tr>
</tbody>
</table>
Age Distribution by Treatment Group – All Clinical Studies
(C-04-38, C-04-40, C-07-40)

<table>
<thead>
<tr>
<th>Age Distribution</th>
<th>Total N (%)</th>
<th>Moxi AF N (%)</th>
<th>Vigamox N (%)</th>
<th>Vehicle N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2535 (100.0)</td>
<td>1270 (100.0)</td>
<td>349 (100.0)</td>
<td>916 (100.0)</td>
</tr>
<tr>
<td>Infants (≥ 1 to &lt; 2 months)*</td>
<td>8 (0.3)</td>
<td>1 (0.1)</td>
<td>2 (0.6)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>Infants (≥ 2 to &lt; 3 months)</td>
<td>4 (0.2)</td>
<td>3 (0.2)</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Infants (≥ 3 to &lt; 4 months)</td>
<td>7 (0.3)</td>
<td>3 (0.2)</td>
<td>0 (0.0)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Infants (≥ 4 to &lt; 5 months)</td>
<td>11 (0.4)</td>
<td>10 (0.8)</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Infants (≥ 5 to &lt; 12 months)</td>
<td>77 (3.0)</td>
<td>41 (3.2)</td>
<td>3 (0.9)</td>
<td>33 (3.6)</td>
</tr>
<tr>
<td>Toddlers (12 to 23 months)</td>
<td>114 (4.5)</td>
<td>59 (4.6)</td>
<td>1 (0.3)</td>
<td>54 (5.9)</td>
</tr>
<tr>
<td>Children (2 to 11 years)</td>
<td>651 (25.7)</td>
<td>317 (25.0)</td>
<td>26 (7.4)</td>
<td>308 (33.6)</td>
</tr>
<tr>
<td>Adolescents (12 to 17 years)</td>
<td>241 (9.5)</td>
<td>110 (8.7)</td>
<td>24 (6.9)</td>
<td>107 (11.7)</td>
</tr>
<tr>
<td>Adults (18 to 64 years)</td>
<td>1250 (49.3)</td>
<td>646 (50.9)</td>
<td>262 (75.1)</td>
<td>342 (37.3)</td>
</tr>
<tr>
<td>Elderly (65 years and older)</td>
<td>172 (6.8)</td>
<td>80 (6.3)</td>
<td>31 (8.9)</td>
<td>61 (6.7)</td>
</tr>
</tbody>
</table>

*Patients under 1 month of age were not enrolled in Studies C-04-38, C-04-40 and C-07-40.

6.1.3 Subject Disposition

Study C-07-40 Subject Disposition

Figure 11.1.1:
Disposition of Patients Enrolled in C-07-40

<table>
<thead>
<tr>
<th>Type of Analysis</th>
<th>Data Set</th>
<th>Exclusions</th>
<th>Type of Analysis</th>
<th>Data Set</th>
<th>Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td>Intent-to-Treat</td>
<td></td>
<td></td>
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<tr>
<td>Evaluable for Safety Analysis (N=1179)</td>
<td>Moxi AF (593)</td>
<td>Veh (586)</td>
<td>Evaluable for ITT Analysis (N=1179)</td>
<td>Moxi AF (593)</td>
<td>Veh (586)</td>
</tr>
<tr>
<td>Excluded from Safety Analysis (N=59)</td>
<td>Moxi AF (0)</td>
<td>Veh (1)</td>
<td>Excluded from ITT Analysis (N=59)</td>
<td>Moxi AF (0)</td>
<td>Veh (1)</td>
</tr>
<tr>
<td>Microbiological</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent-to-Treat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable for MBITT Analysis (N=847)</td>
<td>Moxi AF (424)</td>
<td>Veh (423)</td>
<td>Evaluable for MITT Analysis (N=839)</td>
<td>Moxi AF (415)</td>
<td>Veh (414)</td>
</tr>
<tr>
<td>Excluded from MBITT Analysis (N=132)</td>
<td>Moxi AF (169)</td>
<td>Veh (163)</td>
<td>Excluded from MITT Analysis (N=50)</td>
<td>Moxi AF (178)</td>
<td>Veh (128)</td>
</tr>
<tr>
<td>Per Protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable for PP Analysis (N=1128)</td>
<td>Moxi AF (567)</td>
<td>Veh (561)</td>
<td>Evaluable for MPP Analysis (N=814)</td>
<td>Moxi AF (406)</td>
<td>Veh (408)</td>
</tr>
<tr>
<td>Excluded from PP Analysis (N=51)</td>
<td>Moxi AF (26)</td>
<td>Veh (25)</td>
<td>Excluded from MPP Analysis (N=314)</td>
<td>Moxi AF (161)</td>
<td>Veh (153)</td>
</tr>
<tr>
<td>Modified Per Protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable for MPP Analysis (N=814)</td>
<td>Moxi AF (406)</td>
<td>Veh (408)</td>
<td>Evaluable for MPP Analysis (N=314)</td>
<td>Moxi AF (161)</td>
<td>Veh (153)</td>
</tr>
<tr>
<td>Excluded from MPP Analysis (N=314)</td>
<td>Moxi AF (161)</td>
<td>Veh (153)</td>
<td>Excluded from MPP Analysis (N=314)</td>
<td>Moxi AF (161)</td>
<td>Veh (153)</td>
</tr>
</tbody>
</table>

Reference ID: 2866357
6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for study C-07-40 was the clinical cure rate of the two ocular signs of bacterial conjunctival infection (bulbar conjunctival injection and conjunctival discharge/exudate) at the EOT/Exit Visit (Day 4). Clinical cure was attained when the sum of the two ocular signs was zero. The primary microbiological endpoint was the bacterial eradication rate at the EOT/Exit Visit (Day 4).

The primary statistical objective for study C-07-40 was to demonstrate that moxifloxacin AF was superior to vehicle in the treatment of bacterial conjunctivitis.

Analysis Populations:

Safety: All patients who received drug.

Intent-to-Treat (ITT): All patients who received drug and had at least one on-therapy visit.

Microbiological Intent-to-Treat (MBITT): All patients who received drug, had at least one on-therapy visit and were pathogen positive for bacteria on Day 1.

Modified Intent-to-Treat (MITT): All patients who received drug, had at least one on-therapy visit, met pre-randomization inclusion and exclusion criteria and were pathogen positive for bacteria on Day 1.

Per Protocol (PP): All patients who received drug, met pre-randomization inclusion and exclusion criteria and had baseline and test of cure (or exit if the patient exited from the study early) visits.

Modified Per Protocol (MPP): All patients who received drug, met pre-randomization inclusion and exclusion criteria, had baseline and test of cure (or exit if the patient exited from the study early) visits and were pathogen positive for bacteria on Day 1.

The planned primary efficacy endpoints for this study were clinical cure (bulbar conjunctival injection+0, normal and conjunctival discharge/exudate=0, absent) and microbiological success (bacterial eradication of pre-therapy pathogens) at the Day 4 [(EOT)/exit] Visit.

**Study C-07-40**

<table>
<thead>
<tr>
<th></th>
<th>Clinical Cure at Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MBITT</td>
</tr>
<tr>
<td>Moxifloxacin AF</td>
<td>265/424 (62.5%)</td>
</tr>
<tr>
<td>Vehicle</td>
<td>214/423 (50.6%)</td>
</tr>
</tbody>
</table>

Reference ID: 2866357
Clinical Review
Lucious Lim, M.D., M.P.H.
NDA 22-428
Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

<table>
<thead>
<tr>
<th>p-value</th>
<th>0.0005</th>
<th>0.0006</th>
<th>0.0002</th>
<th>0.0015</th>
<th>0.0005</th>
</tr>
</thead>
</table>

### Microbiological Success at Day 4

<table>
<thead>
<tr>
<th></th>
<th>MBITT</th>
<th>MITT</th>
<th>MPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin AF</td>
<td>316/424 (74.5%)</td>
<td>308/415 (74.2%)</td>
<td>285/385 (74.0%)</td>
</tr>
<tr>
<td>Vehicle</td>
<td>237/423 (56.0%)</td>
<td>231/414 (55.8%)</td>
<td>220/384 (57.3%)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

**Reviewer’s Comments:**

The Agency informed the applicant during development that the MBITT population would be used for the efficacy evaluation. Moxifloxacin AF dosed two times a day demonstrates superiority to its vehicle in Study C-07-40 for clinical efficacy at Day 4 (p= 0.0005). The clinical cure rate for Moxifloxacin AF was 62.5%. The ITT, MITT, PP and MPP population results are consistent with the MBITT population.

Microbiological efficacy was demonstrated at Day 4 in the MBITT, MITT, and MPP populations (< 0.0001). The microbiological eradication rate for moxifloxacin AF was 74.5%.

#### 6.1.5 Analysis of Secondary Endpoints(s)

The planned secondary endpoints for this study included the eight individual sign and symptom cure rates (bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia) at Day 3 and Day 4 (EOT)/Exit Visits and sustained clinical cure at the Day 3 Visit. A cure for an individual ocular sign or symptom was attained if the score was zero (i.e., absent or normal) and remained zero (for Day 3 findings) throughout the rest of the study. Likewise, sustained clinical cure at the Day 3 Visit was attained if the score was zero (i.e., absent or normal) and remained zero throughout the rest of the study.

After adjusting for multiplicity, bulbar conjunctival injection in the MBITT and MITT populations and conjunctival discharge/exudate in the ITT population demonstrated statistical significance. No other secondary endpoints achieved statistical significance.

**Reviewer’s Comments:**

Significance of these two secondary endpoints is expected since bulbar conjunctival injection and conjunctival discharge/exudate are the 2 cardinal signs of bacterial conjunctivitis.
6.1.6 Other Endpoints

Exploratory Analyses included and evaluation of an earlier clinical cure at Day 3. Clinical cure was attained if the sum of the 2 cardinal ocular signs of bacterial conjunctivitis was zero (i.e., normal or absent) and remained zero throughout the course of the study.

**Study C-07-40**

<table>
<thead>
<tr>
<th>Clinical Cure at Day 3</th>
<th>MBITT</th>
<th>ITT</th>
<th>MITT</th>
<th>PP</th>
<th>MPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin AF</td>
<td>71/424 (16.7%)</td>
<td>101/593 (17.0%)</td>
<td>71/415 (17.1%)</td>
<td>99/561 (17.6%)</td>
<td>72/401 (18.0%)</td>
</tr>
<tr>
<td>Vehicle</td>
<td>56/423 (13.2%)</td>
<td>88/586 (15.0%)</td>
<td>53/414 (12.8%)</td>
<td>84/551 (15.2%)</td>
<td>53/398 (13.3%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.1529</td>
<td>0.3457</td>
<td>0.0822</td>
<td>0.2801</td>
<td>0.0711</td>
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</tbody>
</table>

**Reviewer’s Comments:**

*Moxifloxacin AF failed to demonstrate clinical efficacy versus its vehicle at Day 3 in all study populations.*

6.1.7 Subpopulations

The primary efficacy endpoint (clinical cure and microbiological success at Day 4 (EOT)/Exit Visit) were analyzed separately by investigator and for each of the following demographic subgroups in study C-07-40: age (28 days to 23 months, 2-11 years, 12-17 years, 18-64 years and age ≥ 65), sex, race, ethnicity, iris color, affected eye(s) and study eye. These analyses were performed in the ITT, MBITT, MITT, PP, and MPP data sets.

**MBITT – Clinical Cure at Day 4 (EOT) - Study C-07-40**

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment</th>
<th>Total</th>
<th>Clinical Cure</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 days – 23 months</td>
<td>Moxifloxacin AF</td>
<td>44</td>
<td>33</td>
<td>75.0</td>
</tr>
<tr>
<td></td>
<td>Vehicle</td>
<td>43</td>
<td>24</td>
<td>55.8</td>
</tr>
<tr>
<td>2-11 years</td>
<td>Moxifloxacin AF</td>
<td>129</td>
<td>96</td>
<td>56.0</td>
</tr>
<tr>
<td></td>
<td>Vehicle</td>
<td>134</td>
<td>75</td>
<td>51.4</td>
</tr>
<tr>
<td>12-17 years</td>
<td>Moxifloxacin AF</td>
<td>43</td>
<td>24</td>
<td>55.8</td>
</tr>
<tr>
<td></td>
<td>Vehicle</td>
<td>45</td>
<td>24</td>
<td>53.3</td>
</tr>
<tr>
<td>18-64 years</td>
<td>Moxifloxacin AF</td>
<td>175</td>
<td>95</td>
<td>54.3</td>
</tr>
<tr>
<td></td>
<td>Vehicle</td>
<td>159</td>
<td>77</td>
<td>48.4</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>Moxifloxacin AF</td>
<td>33</td>
<td>17</td>
<td>51.5</td>
</tr>
<tr>
<td></td>
<td>Vehicle</td>
<td>42</td>
<td>14</td>
<td>33.3</td>
</tr>
</tbody>
</table>

Reference ID: 2866357
Clinical Review
Lucious Lim, M.D., M.P.H.
NDA 22-428
Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

---

**MBITT – Microbiological Success at Day 4 (EOT) - Study C-07-40**

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment</th>
<th>N</th>
<th>N</th>
<th>%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 days – 23 months</td>
<td>Moxifloxacin AF</td>
<td>44</td>
<td>34</td>
<td>77.3</td>
<td>0.0016</td>
</tr>
<tr>
<td></td>
<td>Vehicle</td>
<td>43</td>
<td>19</td>
<td>44.2</td>
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</tr>
<tr>
<td>2-11 years</td>
<td>Moxifloxacin AF</td>
<td>129</td>
<td>107</td>
<td>82.9</td>
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</tr>
<tr>
<td></td>
<td>Vehicle</td>
<td>134</td>
<td>78</td>
<td>58.2</td>
<td></td>
</tr>
<tr>
<td>12-17 years</td>
<td>Moxifloxacin AF</td>
<td>43</td>
<td>30</td>
<td>69.8</td>
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<tr>
<td></td>
<td>Vehicle</td>
<td>45</td>
<td>34</td>
<td>75.6</td>
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</tr>
<tr>
<td>18-64 years</td>
<td>Moxifloxacin AF</td>
<td>175</td>
<td>122</td>
<td>69.7</td>
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<tr>
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<td>Vehicle</td>
<td>159</td>
<td>93</td>
<td>58.5</td>
<td></td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>Moxifloxacin AF</td>
<td>33</td>
<td>23</td>
<td>69.7</td>
<td>0.0009</td>
</tr>
<tr>
<td></td>
<td>Vehicle</td>
<td>42</td>
<td>13</td>
<td>31.0</td>
<td></td>
</tr>
</tbody>
</table>

**Reviewer’s Comments:**

In general, the results of the subgroup analysis for Study C-07-40 follow the same trend as the overall efficacy analysis. The primary endpoint of clinical cure and microbiological success at Day 4 appears to be driven by the 2-11 age group subset.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The concentration of 0.5% moxifloxacin was chosen for Moxifloxacin AF based on the efficacy and safety of Vigamox. The modified formulation contains a xanthan gum of the product on the ocular surface with the objective of maintaining similar efficacy to Vigamox with reduced dosing (i.e. two times a day versus three times a day).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In Study C-07-40, patients were evaluated at the End-of-Therapy Visit approximately 12-48 hours following the last dose and in Studies C-04-38 and C-04-40, patients were evaluated at a Test-of-Cure Visit approximately 60-90 hours following the last dose. No evidence of tolerance or withdrawal effects was detected.

6.1.10 Additional Efficacy Issues/Analyses

Reference ID: 2866357
Clinical Cure by Organism for patients Treated with Moxifloxacin AF
Studies C-04-38, C-04-40, and C-07-40 Combined (MBITT Population)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Total (N)</th>
<th>Clinical Cure (n)</th>
<th>Clinical Failure (n)</th>
<th>Eradication Rate (%)</th>
</tr>
</thead>
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<td><strong>Gram - positive</strong></td>
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<td></td>
</tr>
<tr>
<td>Aerococcus viridans*</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Corynebacterium macginleyi*</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Enterococcus faecalis*</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Micrococcus luteus*</td>
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<td>6</td>
<td>0</td>
<td>100</td>
</tr>
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<td>Staphylococcus arlettae*</td>
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<td>93</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus</td>
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<td>3</td>
<td>77</td>
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<td>Staphylococcus hominis²</td>
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<td>100</td>
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<tr>
<td>Staphylococcus saprophyticus*</td>
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<td>6</td>
<td>0</td>
<td>100</td>
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<td>Staphylococcus warneri*</td>
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<td>8</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>Streptococcus mitis*</td>
<td>11</td>
<td>9</td>
<td>2</td>
<td>82</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>43</td>
<td>39</td>
<td>4</td>
<td>91</td>
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<td>Streptococcus parasanguinis*</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td><strong>Gram - negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli*</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>83</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>109</td>
<td>100</td>
<td>9</td>
<td>92</td>
</tr>
<tr>
<td>Klebsiella pneumoniae*</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td><strong>Anaerobe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>152</td>
<td>139</td>
<td>13</td>
<td>91</td>
</tr>
<tr>
<td><strong>Other bacteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlamydia trachomatis*</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

* Efficacy for this organism was found in fewer than 10 infections.
¹ Includes Staphylococcus capitis subspecies capitis (3), S. capitis (22); eradication rate 100% and 96 % respectively.
² Includes Staphylococcus hominis ss. novobiosepticus (4), S. hominis (6); eradication rate 100%

7 Review of Safety

Safety Summary

7.1 Methods
### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Study Design</th>
<th>Subject/Patient Population</th>
<th>Treatment Groups</th>
<th>Dosing Regimen</th>
<th>Dosing duration</th>
<th>Total No. Subjects/Patients Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-07-12</td>
<td>Single topical ocular dose conjunctiva/aqueous humor PK study</td>
<td>Cataract surgery patients</td>
<td>Moxifloxacin AF ophthalmic solution</td>
<td>1 drop</td>
<td>Single dose</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vigamox</td>
<td>1 drop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-05-15</td>
<td>Multiple topical ocular dosing systemic PK/safety study</td>
<td>Healthy adult male and female volunteers</td>
<td>Moxifloxacin AF ophthalmic solution</td>
<td>1 drop BID OU</td>
<td>4 days with final dose on Day 5</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vehicle</td>
<td>1 drop BID OU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-04-38</td>
<td>Safety/efficacy study</td>
<td>Patients 1 month of age and older with bacterial conjunctivitis</td>
<td>Moxifloxacin AF ophthalmic solution</td>
<td>1 drop BID OU</td>
<td>3 days</td>
<td>661 (345 culture positive diagnosed eye)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vehicle</td>
<td>1 drop BID OU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-04-40</td>
<td>Safety/efficacy study</td>
<td>Patients 1 month of age and older with bacterial conjunctivitis</td>
<td>Moxifloxacin AF ophthalmic solution</td>
<td>1 drop BID OU</td>
<td>3 days</td>
<td>695 (382 culture positive diagnosed eye)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and Vehicle</td>
<td>1 drop BID OU</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vigamox</td>
<td>1 drop TID OU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-07-40</td>
<td>Safety/efficacy study</td>
<td>Patients 1 month of age and older with bacterial conjunctivitis</td>
<td>Moxifloxacin AF ophthalmic solution</td>
<td>1 drop BID OU</td>
<td>3 days</td>
<td>1179 (847 culture positive diagnosed eye)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vehicle</td>
<td>1 drop BID OU</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7.1.2 Categorization of Adverse Events

Routine clinical testing was required to establish the safety of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.). This was adequately addressed in the design and conduct of the clinical trials. All adverse events were coded using a MedDRA dictionary and received independent causality assessments from the Investigator and the Medical Monitor.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Due to the size of the data base, the pooled data was used in the analysis of common adverse events. Adverse events for each study were also evaluated individually.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 1355 patients were exposed to moxifloxacin AF during development.

**Overview of Exposure to Study Drug by Protocol**

<table>
<thead>
<tr>
<th>Protocol Number</th>
<th>Safety N</th>
<th>Moxi AF</th>
<th>Vigamox</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-07-40</td>
<td>1177</td>
<td>593</td>
<td></td>
<td>586</td>
</tr>
<tr>
<td>C-04-38</td>
<td>661</td>
<td>331</td>
<td></td>
<td>330</td>
</tr>
<tr>
<td>C-04-40</td>
<td>695</td>
<td>346</td>
<td></td>
<td>349</td>
</tr>
<tr>
<td>C-05-15</td>
<td>30</td>
<td>20</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>C-07-12</td>
<td>130</td>
<td>65</td>
<td></td>
<td>65</td>
</tr>
</tbody>
</table>

The age distribution of the patients exposed to moxifloxacin during development is as follows:

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 days to 23 months</td>
<td>117</td>
</tr>
<tr>
<td>2 to 11 years</td>
<td>317</td>
</tr>
<tr>
<td>12 to 17 years</td>
<td>109</td>
</tr>
<tr>
<td>18 to 64 years</td>
<td>675</td>
</tr>
<tr>
<td>65 years or older</td>
<td>127</td>
</tr>
</tbody>
</table>
Reviewer’s Comments:

The majority (58-95.7%) of patients in each age group were exposed to moxifloxacin AF for 3 days with another 2-5% exposed to a total of 4 days of drug.

7.2.2 Explorations for Dose Response

Moxifloxacin AF was administered in one dose level (1 drop twice a day for three days) for each of the phase 3 studies. No dose response information was obtained.

7.2.3 Special Animal and/or In Vitro Testing

No special toxicology studies were conducted with Moxifloxacin AF.

7.2.4 Routine Clinical Testing

The routine clinical testing required to evaluate the safety concerns of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of this clinical trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

Based on in vitro studies conducted on moxifloxacin and contained in the original NDA, moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19 or CYP1A2 and therefore is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 isozymes.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events reported during the development of moxifloxacin AF are consistent with other topical quinolones. The assessment of these adverse events in the clinical trials were adequate.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during the clinical development of moxifloxacin AF.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events were reported during the clinical development of moxifloxacin AF.
7.3.3 Dropouts and/or Discontinuations

<table>
<thead>
<tr>
<th>Reason for Discontinuation</th>
<th>C-07-40</th>
<th>C-04-38</th>
<th>C-04-40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>Moxi AF</td>
<td>Vehicle</td>
<td>Moxi AF</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>3</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Patient’s decision unrelated to an adverse event</td>
<td>3</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Noncompliance</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>6</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Moxi AF = Moxifloxacin AF

A Table of the adverse events associated with the discontinuations from each of the clinical study is presented below.

**Adverse Events Associated with Discontinuation – Study C-07-40**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Treatment</th>
<th>Onset day</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>9507</td>
<td>76</td>
<td>F</td>
<td>Moxifloxacin AF</td>
<td>2</td>
<td>Eye irritation</td>
</tr>
</tbody>
</table>

**Adverse Events Associated with Discontinuation – Study C-04-38**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Treatment</th>
<th>Onset day</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1720</td>
<td>48</td>
<td>F</td>
<td>Moxifloxacin AF</td>
<td>1</td>
<td>Foreign body sensation, increased lacrimation, conjunctival disorder</td>
</tr>
<tr>
<td>2005</td>
<td>32</td>
<td>M</td>
<td>Moxifloxacin AF</td>
<td>2</td>
<td>gonorrhea</td>
</tr>
<tr>
<td>1314</td>
<td>19</td>
<td>F</td>
<td>Moxifloxacin AF</td>
<td>2</td>
<td>Streptococcal pharyngitis</td>
</tr>
<tr>
<td>2218</td>
<td>1</td>
<td>M</td>
<td>Moxifloxacin AF</td>
<td>5</td>
<td>Sinusitis</td>
</tr>
<tr>
<td>102</td>
<td>15</td>
<td>M</td>
<td>Moxifloxacin AF</td>
<td>3</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>405</td>
<td>1</td>
<td>M</td>
<td>Vehicle</td>
<td>2</td>
<td>Otitis Media</td>
</tr>
<tr>
<td>1312</td>
<td>3</td>
<td>M</td>
<td>Vehicle</td>
<td>4</td>
<td>Otitis media</td>
</tr>
<tr>
<td>2126</td>
<td>2</td>
<td>M</td>
<td>Vehicle</td>
<td>1</td>
<td>Periorbital cellulitis</td>
</tr>
<tr>
<td>926</td>
<td>42</td>
<td>F</td>
<td>Vehicle</td>
<td>5</td>
<td>conjunctivitis</td>
</tr>
<tr>
<td>104</td>
<td>41</td>
<td>M</td>
<td>Vehicle</td>
<td>4</td>
<td>Uveitis</td>
</tr>
</tbody>
</table>

Reference ID: 2866357
Adverse Events Associated with Discontinuation – Study C-04-40

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Treatment</th>
<th>Onset day</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>3413</td>
<td>21</td>
<td>M</td>
<td>Moxifloxacin AF</td>
<td>2</td>
<td>Conjunctival edema, eyelid edema, ocular hyperemia</td>
</tr>
<tr>
<td>2422</td>
<td>41</td>
<td>M</td>
<td>Moxifloxacin AF</td>
<td>6</td>
<td>Conjunctival ulcer</td>
</tr>
<tr>
<td>4007</td>
<td>9</td>
<td>M</td>
<td>Moxifloxacin AF</td>
<td>1</td>
<td>Rhinitis, corneal opacity, punctuate keratitis, nasal congestion, pyrexia</td>
</tr>
<tr>
<td>3408</td>
<td>24</td>
<td>M</td>
<td>Vigamox</td>
<td>3</td>
<td>Conjunctival edema, eye pruritus, eyelid edema</td>
</tr>
</tbody>
</table>

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuation are presented in section 7.3.3. There were no other significant adverse events identified.

7.3.5 Submission Specific Primary Safety Concerns

N/A – No specific safety issues identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common Adverse Events (rate ≥ 1%) – Safety Population (Studies C-04-38, C-04-408, C-05-15, C-07-12, C-07-40 Pooled)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Moxifloxacin AF N=1355</th>
<th>Vigamox N=414</th>
<th>Vehicle N=926</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye irritation</td>
<td>16</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>14</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Eye Pain</td>
<td>14</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Eye pruritis</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

Reference ID: 2866357
**Clinical Review**  
Lucious Lim, M.D., M.P.H.  
NDA 22-428  
Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

<table>
<thead>
<tr>
<th>site conditions</th>
<th>Pyrexia</th>
<th>16</th>
<th>1.2</th>
<th>7</th>
<th>1.7</th>
<th>6</th>
<th>0.6</th>
</tr>
</thead>
</table>

**Infections and infestations**

<p>| | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctivitis</td>
<td>8</td>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bacterial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otitis media</td>
<td>4</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>8</td>
<td>0.6</td>
<td>2</td>
<td></td>
<td>0.5</td>
<td>10</td>
<td>1.1</td>
</tr>
</tbody>
</table>

**Common Adverse Events (rate ≥ 1%) – Safety Population – study C-07-40**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Moxifloxacin AF N=331</th>
<th>Vehicle N=330</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis bacterial</td>
<td>8</td>
<td>1.3</td>
</tr>
</tbody>
</table>

**Common Adverse Events (rate ≥ 1%) – Safety Population – study C-04-38**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Moxifloxacin AF N=331</th>
<th>Vehicle N=330</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>5</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6</td>
<td>1.8</td>
</tr>
<tr>
<td>Otitis media</td>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 2866357
Clinical Review
Lucious Lim, M.D., M.P.H.
NDA 22-428
Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

<table>
<thead>
<tr>
<th>Headache</th>
<th>0</th>
<th>0</th>
<th>6</th>
<th>1.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2</td>
<td>0.6</td>
<td>4</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Common Adverse Events (rate ≥ 1%) – Safety Population – study C-04-40

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Moxifloxacin AF N=346</th>
<th>Vigamox N=349</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye irritation</td>
<td>8</td>
<td>2.3</td>
</tr>
<tr>
<td>Eye pain</td>
<td>8</td>
<td>2.3</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td>Punctuate keratitis</td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7</td>
<td>2.0</td>
</tr>
</tbody>
</table>

7.4.2 Laboratory Findings

Clinical laboratory evaluations were analyzed in one pharmacokinetic study (C-05-15) which involved 30 healthy male and female patients (19 to 73 years of age). Laboratory test including hematology, blood chemistry and urinalysis results were evaluated in all patients at baseline and exit.

There were statistically significant changes from baseline for both moxifloxacin AF and the vehicle in several hematology and blood chemistry parameters. However, these changes were not clinically relevant and each remained within the normal range.

There were no statistically significant changes in urinalysis measurements for either moxifloxacin AF or the vehicle.

7.4.3 Vital Signs

Cardiovascular parameters (pulse and blood pressure) were measured at screening, day 1 and the exit visit. Any clinically relevant changes from baseline were reported as an adverse event. No adverse events were reported for the cardiovascular parameters during the study. No clinically relevant changes in cardiovascular parameters were observed. No clinically relevant differences between the treatment groups were identified.
7.4.4 Electrocardiograms (ECGs)

Twelve-lead ECGs were obtained at baseline and the exit visit. There were no clinically relevant changes reported within groups or between groups for moxifloxacin and the vehicle group.

7.4.5 Special Safety Studies/Clinical Trials

N/A – There were no special safety studies conducted for this product.

7.4.6 Immunogenicity

N/A – Immunogenicity testing was not conducted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Moxifloxacin AF was administered in one dose level (1 drop twice a day for three days) for each of the phase 3 studies. No dose response information was obtained.

7.5.2 Time Dependency for Adverse Events

N/A – Moxifloxacin does not have a delayed onset of action. Exploration of time to onset was not conducted.

7.5.3 Drug-Demographic Interactions

Demographic subgroups with and without adverse events were sorted by age, gender, race, ethnicity. Based on a review of adverse events by these subgroups, the events are consistent with the overall safety population.

7.5.4 Drug-Disease Interactions

A review of adverse events reveal no untoward safety issues in each of the subpopulations categorized by concomitant diseases.

7.5.5 Drug-Drug Interactions

No drug interactions were reported in any clinical study involving Moxifloxacin AF.
Clinical Review
Lucious Lim, M.D., M.P.H.
NDA 22-428
Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies have not been conducted. In addition, long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. An accelerated study with initiators and promoters was conducted in rats and moxifloxacin was not found to be carcinogenic. (See original review/label for Vigamox).

7.6.2 Human Reproduction and Pregnancy Data

The clinical study protocols involving moxifloxacin AF excluded the participation of pregnant or breast-feeding females. No information was obtained on its use in these populations.

7.6.3 Pediatrics and Assessment of Effects on Growth

Based on the review of the original NDA for Vigamox, there is no evidence that the ophthalmic administration of moxifloxacin has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No information is available on overdosage in humans. No reports of overdose were received during the clinical studies of moxifloxacin AF. In an oral (gavage) monkey study of moxifloxacin, doses up to 15mg/kg/day did not produce any toxicity. This dose is at least ten times higher than the accidental dose of one bottle of moxifloxacin AF, 5 mg/mL for a 10 kg child.

There was no evidence of drug abuse reported in the clinical trials. And there were no reports of withdrawal or rebound phenomena.

7.7 Additional Submissions / Safety Issues

The four-month safety update was received on September 28, 2010. There was no new information to report.

8 Postmarket Experience

Moxifloxacin AF is not marketed in any country. Moxifloxacin hydrochloride ophthalmic solution, 0.5% base is approved in more than 50 countries. It was approved in the U.S. in 2003.
The sponsor has received 471 spontaneous adverse event reports worldwide associated with moxifloxacin. Thirty-five (35) were considered serious. The spontaneous postmarketing reports for moxifloxacin are consistent with its known safety profile. A review of the postmarketing reports does not raise concern that there is a new unknown safety risk associated with moxifloxacin.
9 Appendices

9.1 Literature Review/References

N/A – An independent literature review was not conducted for this application.

9.2 Labeling Recommendations

See labeling recommendations which follow in the attached label.

9.3 Advisory Committee Meeting

N/A – An advisory committee meeting is not required for this application.

10 Page(s) of Draft Labeling Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LUCIOUS LIM
11/19/2010

WILLIAM M BOYD
11/19/2010

Reference ID: 2866357