CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205572Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	March 19, 2015
To:	Sumathi Nambiar, MD, MPH Director **Division of Anti-Infective Products (DAIP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	Moxifloxacin Injection
Dosage Form and Route:	Solution, for intravenous use
Application Type/Number:	NDA 205-572
Applicant:	Fresenius Kabi USA, LLC

1 INTRODUCTION

On October 3, 2014, Fresenius Kabi USA LLC, re-submitted for the Agency's review a New Drug Application (NDA 205-572) for moxifloxacin injection, solution for intravenous use, a fluoroquinolone antibacterial indicated for treating infections in adults (18 years of age and older) caused by designated susceptible bacteria. This NDA was originally submitted on June 06, 2013, but received a Complete Response (CR) letter from the Agency on April 04, 2014, citing DMF deficiencies.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Anti-Infective Products (DAIP) on January 12, 2015, for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) for moxifloxacin injection, solution for intravenous use.

2 MATERIAL REVIEWED

- Draft moxifloxacin injection MG received on October 03, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on March 16, 2015.
- Draft moxifloxacin injection Prescribing Information (PI) received on October 03, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on March 16, 2015.
- Approved AVELOX (moxifloxacin hydrochloride) comparator labeling dated November 20, 2014.

3 REVIEW METHODS

In our focused review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG is consistent with the Avelox comparator labeling and fluoroquinolone class language where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Consult DMPP during the next review cycle for a comprehensive review of the Patient Labeling to make it fully consistent with Patient Labeling standards.

- Our focused review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
03/19/2015

MARCIA B WILLIAMS
03/19/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 17, 2015
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 205572
Product Name and Strength:	Moxifloxacin Injection 400 mg/250 ml (1.6 mg/mL)
Submission Date:	March 6, 2015
Applicant/Sponsor Name:	Fresenius Kabi
OSE RCM #:	2014-2198-01
DMEPA Primary Reviewer:	Jacqueline Sheppard, PharmD
DMEPA Acting Team Leader:	Vicky Borders-Hemphill, PharmD
DMEPA Associate Director :	Irene Z. Chan, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Anti-Infective Products (DAIP) requested that we review container labels and overwrap labeling (Appendix A) for Moxifloxacin Injection, 400 mg/250 mL (1.6 mg/mL), to determine if they are acceptable from a medication error perspective. Fresenius Kabi submitted an email dated March 6, 2015, describing their rationale for not making recommended revisions (Appendix B) that we provided in a previous label and labeling review.[1] We address these responses and make additional recommendations below.

[1] Sheppard J. Label and Labeling Review for Moxifloxacin (NDA 205572). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Feb 20. 9 p. OSE RCM No.: 2014-2198.

2 DISCUSSION

We acknowledge that Fresenius Kabi provided comments in response to each of the three labeling recommendations we provided in our previous label and labeling review. We find their rationale for two of the three recommendations unacceptable and provide our rationale below. Each recommendation, along with a summary of the Sponsor's reply, is detailed below and we provide our response to the proposed status of each recommendation:

1. ***Please ensure that the entire name, which includes the dosage form, appears in a single font.***

Sponsor Response: Fresenius Kabi stated that they would like to maintain the current font and design of the entire drug product name on the bag and overlap. The Sponsor stated that their label design provides the same level of prominence as the currently approved Reference listed drug (RLD) product.

DMEPA Response: We agree that the critical components of the drug products including drug name and strength have sufficient prominence on the label. We find Fresenius Kabi's proposal to maintain their current font and design of the drug name acceptable.

2. ***Increase the prominence of important storage information by capitalizing the statement "DO NOT REFRIGERATE – PRODUCT PRECIPITATES UPON REFRIGERATION"***

Sponsor Response: Fresenius Kabi has agreed to increase the prominence on both the bag label and overwrap labeling as per the Agency's request but would like to implement the change in the next production campaign following the initial launch quantity.

DMEPA Response: We have been informed that additional changes will be recommended by other disciplines, thus, we recommend that the prominence of the storage information on both the bag label and overwrap labeling be implemented along with the other changes prior to approval of this NDA.

3. ***Remove*** [redacted] (b) (4) ***as it may pose dosing confusion and be misinterpreted as the total volume of the bag.***

Sponsor Response: Fresenius Kabi has stated that [redacted] (b) (4) and, as such, the second presentation is an additional cue to allow practitioners to distinguish between moxifloxacin and other antibiotics available in similar volume bags. Fresenius Kabi also stated that standard practice is to deliver the entire contents of the bag; [redacted] (b) (4) is minimizing medication errors.

DMEPA Response: We disagree with the assertion by Fresenius Kabi that the [redacted] (b) (4) will minimize medication errors and find the second presentation of the [redacted] (b) (4) statement unacceptable. We recommend that the additional [redacted] (b) (4) be removed. This additional statement is an [redacted] (b) (4) statement and would mislabel the product since the [redacted] (b) (4) should be expressed as the [redacted] (b) (4) in

accordance with the USP General Chapter <1> INJECTIONS. We provide recommendations in Section 3.

3 CONCLUSION & RECOMMENDATIONS

We conclude the Sponsor can improve the proposed labels and labeling to increase clarity and prominence of important information to promote safe use of this product. Thus, the container label and overwrap labeling for Moxifloxacin Injection are unacceptable from a medication error perspective. We recommend the following be implemented prior to approval of this NDA:

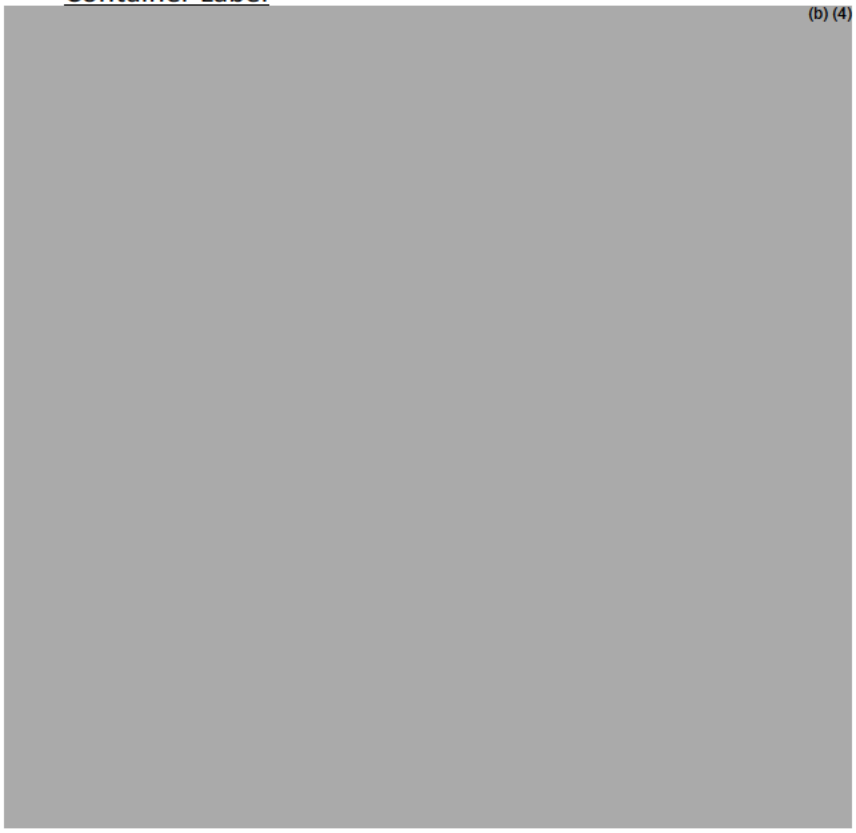
1. Remove [redacted] (b) (4) as this additional statement is an [redacted] (b) (4) statement and would mislabel the product since the [redacted] (b) (4) should be expressed as the [redacted] (b) (4) in accordance with the USP General Chapter <1> INJECTIONS.
2. We have been informed that additional changes will be recommended by other disciplines, thus, we recommend that the prominence of the storage statement be increased by capitalizing each word as follows: "DO NOT REFRIGERATE – PRODUCT PRECIPITATES UPON REFRIGERATION", on both the bag label and overwrap labeling be implemented along with the other changes prior to approval of this NDA.

APPENDIX A. LABEL AND LABELING SUBMITTED ON OCTOBER 2, 2014 AND OCTOBER 22, 2014

- Container Labels (submitted on August 29, 2014)
- Response from Fresenius Kabi (submitted on March 6, 2015)

Container Label

(b) (4)



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APPENDIX B. SPONSOR'S RATIONALE SUBMITTED

Response from Fresenius Kabi

FK USA RESPONSE:

Please find below FK USA's comments to the labeling questions received on March 2, 2015. At this time, FK USA is actively preparing for launch of this critical antibiotic product. Due to the pending PDUFA goal date of April 3, 2015, FK has already manufactured the quantities needed for the initial launch of this product immediately upon approval. It is our understanding from industry and customer discussions that the Moxifloxacin Sodium Injection is in critical supply at the moment. As a result, we have proactively produced our launch supply in an effort to prevent this product from a drug shortage.

1. **Please ensure that the entire name, which includes the dosage form, appears in a single font size.**

At this time, FK USA would like to maintain the current font and design of the entire drug product name on both the bag and overwrap. Due to the limited landscape of the printed area on the 250mL bag and overwrap, FK USA feels that the current label design provides the correct amount of prominence on the critical components of the drug product, including name and strength. In addition, the current RLD label for the Avelox product does not have the entire name, including the dosage form, in a single font size. FK feels that our label design provides the same level of prominence for the drug product name as the currently approved RLD product.

2. **Increase the prominence of important storage information by capitalizing the statement "DO NOT REFRIGERATE – PRODUCT PRECIPITATES UPON REFRIGERATION'.**

FK USA agrees to increase the prominence on both the bag and overwrap labe as per the FDA's request (b) (4) (b) (4)

3. **Remove** (b) (4) **as it may pose dosing confusion and be misinterpreted as the total volume of the bag.**

It is the opinion of FK, USA that the prominent display of (b) (4) *on the drug label is an effective method of minimizing potential medication errors with Moxiflixacin Injection IV bag. based on the following points highlighted below:*

- *The standard practice of administration of the Moxifloxacin IV bag is to deliver the entire contents of the bag in order to deliver the correct dose.*
- (b) (4) *As such, the second presentation of the* (b) (4) *is an additional visual cue that would allow a practitioner to distinguish between Moxifloxacin and other antibiotics that may have a similar name and be available in 250 ml volume IV bag.*
- *Prominent display of the* (b) (4) *is the standard of labeling for antibiotics. This is based on the fact that the dosing for this drug class is not volume based, and the practitioner would expect the* (b) (4) *to be highly visible on the drug label.*
- *We have also received comments from the FDA for other products within the antibiotic class that we need to improve the prominence of the total strength of the product on the bag and overwrap label. In order to properly address these comments, FK has adopted this label design to ensure*

that selection of a product for use is driven by the (b) (4) *and not volume.*

- *Finally, the FK USA Moxifloxacin drug label clearly states the* (b) (4) *in* (b) (4) *as well as* (b) (4) *of the solution. In addition, the* (b) (4) *is prominently emphasized on the label.*

Consequently, FK USA is proposing to maintain the second presentation of the (b) (4) *on the proposed bag and overwrap label.*

Please let me know if you have any questions on this response and if there is a possibility to be put in direct contact with the labeling reviewer within the Division of Medication Errrors. Thank you in advance for your support.
Regards,
Andrea

Andrea Redd
Director, US Regulatory Affairs

Fresenius Kabi USA, LLC
Three Corporate Drive

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/s/

BRENDA V BORDERS-HEMPHILL on behalf of JACQUELINE E SHEPPARD
03/17/2015

BRENDA V BORDERS-HEMPHILL
03/17/2015

IRENE Z CHAN
03/17/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 12, 2015

To: Fariba Izadi, PharmD
Regulatory Health Project Manager
Division of Anti-Infective Products (DAIP)

From: Puja Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Response
NDA 205572
Moxifloxacin Injection, solution for intravenous use

Background

This consult review is in response to DAIP's January 8, 2015, request for OPDP's review of the draft package insert (PI) for Moxifloxacin Injection, solution for intravenous use. OPDP's comments are based on the substantially complete version of the labeling titled, "Moxifloxacin PI 2_2_15.docx" which was accessed via SharePoint on March 11, 2015. Our comments on the PI are included directly on the attached copy of the labeling. OPDP also reviewed the Medication Guide and has no comments at this time.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov

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/s/

PUJA J SHAH
03/12/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 20, 2015
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 205572
Product Name and Strength:	Moxifloxacin, 400 mg/250 ml (b) (4)
Product Type:	Single-strength Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Fresenius Kabi
Submission Date:	August 29, 2014
OSE RCM #:	2014-2198
DMEPA Primary Reviewer:	Jacqueline Sheppard, PharmD
DMEPA Acting Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

The Division of Anti-Infective Products requested that we review the revised Prescribing Information, container labels and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. Fresenius Kabi submitted revised labels and labeling as part of a Class 2 resubmission on August 29, 2014.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B – N/A
Previous DMEPA Reviews	C
Human Factors Study	D – N/A
ISMP Newsletters	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed Prescribing Information, container labels and carton labeling for Moxifloxacin to identify areas of vulnerability that may lead to medication errors. We reviewed Moxifloxacin labels and labeling in OSE review # 2013-1820[1] dated December 17, 2013 and found the proposed labels unacceptable from a medication error perspective. Fresenius Kabi submitted revised labels as part of a Class 2 resubmission on August 29, 2014. The revisions requested in OSE review #2013-1280 were not fully implemented. In addition, we identified the use of (b) (4)

[1] Winiarski A. Label, Labeling and Packaging Review for Moxifloxacin (NDA 205572). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 Dec 17. 9 p. OSE RCM No.: 2013-1820.

[redacted]. This abbreviation may also be confused with the abbreviation [redacted] and cause incorrect route errors. We provide recommendations to improve communication of important information to minimize confusion and improve readability in sections 4.1 and 4.2.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labels and labeling can be improved to increase the readability and prominence of important information and to promote the safe use of the product.

4.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for the Division to consider implementing prior to approval of this NDA:

A. Highlights of Prescribing Information and Full Prescribing Information, Dosage and Administration Sections

1. Revise the "IV" abbreviations to the word "intravenous", as the abbreviation "IV" has been identified on the Institutes for Safe Medications Practices (ISMP's) list of error-prone abbreviations[2].
2. Revise the abbreviation [redacted]

B. Medication Guide

1. See A1.

2. The subsection "How should I store moxifloxacin" is missing. Since some patients may store this product at home for home infusion services and because refrigeration will result in precipitation we recommend adding correct storage information similar to: Store at room temperature, do not refrigerate, keep away from children. We defer to the patient labeling group and the Division for exact language.

[2] http://www.ismp.org/tools/errorproneabbreviations.pdf, Accessed December 13, 2013.

4.2 COMMENTS TO THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Bag Label and Overwrap Labeling

1. Ensure that the entire name, which includes the dosage form, appears in a single font size.
2. Increase the prominence of important storage information by capitalizing the statement "DO NOT REFRIGERATE – PRODUCT PRECIPITATES UPON REFRIGERATION'.
3. Remove [redacted] (b) (4) as it may pose dosing confusion and be misinterpreted as the total volume of the bag.

If you have further questions or need clarifications, please contact Karen Townsend, OSE project manager, at 301-796-5413.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Moxifloxacin that Fresenius Kabi Pharmaceuticals that submitted on August 29, 2014.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Moxifloxacin</th></tr>
<tr><td>Initial Approval Date</td><td>1999</td></tr>
<tr><td>Active Ingredient</td><td>Moxifloxacin</td></tr>
<tr><td>Indication</td><td>Treatment of certain bacterial infections</td></tr>
<tr><td>Route of Administration</td><td>Injection</td></tr>
<tr><td>Dosage Form</td><td>Injection</td></tr>
<tr><td>Strength</td><td>Moxifloxacin 400 mg in 250 ml (b) (4)</td></tr>
<tr><td>Dose and Frequency</td><td>
<table>
<tr><th>Type of Infection</th><th>Dose Every 24 hours</th><th>Duration (days)</th></tr>
<tr><td>Acute Bacterial Sinusitis (1.1)</td><td>400 mg</td><td>10</td></tr>
<tr><td>Acute Bacterial Exacerbation of Chronic Bronchitis (1.2)</td><td>400 mg</td><td>5</td></tr>
<tr><td>Community Acquired Pneumonia (1.3)</td><td>400 mg</td><td>7 to 14</td></tr>
<tr><td>Uncomplicated Skin and Skin Structure Infections (SSSI) (1.4)</td><td>400 mg</td><td>7</td></tr>
<tr><td>Complicated SSSI (1.5)</td><td>400 mg</td><td>7 to 21</td></tr>
<tr><td>Complicated Intra-Abdominal Infections (1.6)</td><td>400 mg</td><td>5 to 14</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td>250 ml flexible plastic containers</td></tr>
<tr><td>Storage</td><td>Controlled Room Temperature</td></tr>
</table>

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive on February 9, 2015 using the terms, Moxifloxacin to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified one previous review[3], and we note that our previous recommendations were not implemented. We provide these recommendations in Section 4.1 and 4.2.

[3] Winiarski A. Label, Labeling and Packaging Review for Moxifloxacin (NDA 205572). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 Dec 17. 9 p. OSE RCM No.: 2013-1820.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[4] along with postmarket medication error data, we reviewed the following Moxifloxacin labels and labeling submitted by Fresenius Kabi on February 11, 2014 and August 29, 2014.

- Container label
- Overwrap labeling
- Prescribing Information
- Medication Guide (no image)

G.2 Label and Labeling Images

Container Label

[4] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JACQUELINE E SHEPPARD
02/20/2015

BRENDA V BORDERS-HEMPHILL
02/20/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 205572 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Moxifloxacin Dosage Form: Sterile Injectable Solution Strengths: 400 mg/250 ml		
Applicant: Fresenius Kabi USA, LLC Agent for Applicant (if applicable):		
Date of Application: 06-06-2013 Date of Receipt: 06-07-2013 Date clock started after UN:		
PDUFA Goal Date: 04-07-2014	Action Goal Date (if different): 04-07-2014	
Filing Date: 08-06-2013	Date of Filing Meeting: 07-25-2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 5-New formulation		
Proposed indication(s)/Proposed change(s): for treating infections in adults ≥ 18 years of age caused by designated, susceptible bacteria. • Acute Bacterial Sinusitis • Acute Bacterial Exacerbation of Chronic Bronchitis • Community Acquired Pneumonia • Skin and Skin Structure Infections: Uncomplicated and Complicated • Complicated Intra-Abdominal Infections		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	x			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	x			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		x		
If yes, explain in comment column.			x	
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:			x	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		x		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		x		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***		x		
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		x		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		x		
If another product has orphan exclusivity, is the product			x	

considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*			x	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		x		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			x	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**x**			
Index: Does the submission contain an accurate comprehensive index?	**x**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible x English (or translated into English) ☐ pagination	**x**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**x**	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	x			
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?		x		
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*		x		There were no clinical studies conducted for this application
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	x			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	x			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			x	electronic
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**x**	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		x		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			x	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?			x	

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If no, request in 74-day letter				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			x	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]			x	
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***			x	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***			x	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	x			
Is the PI submitted in PLR format?[4]	x			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			x	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate	x			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

container labels) consulted to OPDP?				
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	x			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		x		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			x	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			x	
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***			x	

ATTACHMENT

MEMO OF FILING MEETING

DATE: 07-25-13

BLA/NDA/Supp #: 205572

PROPRIETARY NAME: None, Fresenius Kabi does not expect to submit a proprietary name

ESTABLISHED/PROPER NAME: Moxifloxacin

DOSAGE FORM/STRENGTH: 400mg/250 ml Sterile Injectable Solution

APPLICANT: Fresenius Kabi USA, LLC

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Proposed indication(s)/Proposed change(s): for treating infections in adults ≥ 18 years of age caused by designated, susceptible bacteria.
• Acute Bacterial Sinusitis • Acute Bacterial Exacerbation of Chronic Bronchitis • Community Acquired Pneumonia • Skin and Skin Structure Infections: Uncomplicated and Complicated
• Complicated Intra-Abdominal Infections
BACKGROUND: The Sponsor submitted a 505(b(2) application identifying the reference Listed Drug as Avelox manufactured by Bayer.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Fariba Izadi	Y
	CPMS/TL:	Frances LeSane	Y
Cross-Discipline Team Leader (CDTL)	John Alexander		Y
Clinical	Reviewer:	Yulia Yasinskaya	Y
	TL:	John Alexander	
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Kerry Snow	N
	TL:	Kerry Snow	N

Clinical Pharmacology	Reviewer:	Seong Jang	
	TL:	Kim Bergman	
Biostatistics	Reviewer:	Chris Kadoorie	
	TL:	Thamban Valappil	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Terry Miller	
	TL:	Wendy Schmidt	
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	N/A
	TL:		
Product Quality (CMC)	Reviewer:	Milton Sloan	
	TL:	Dorota Mateka	
Quality Microbiology *(for sterile products)*	Reviewer:	Neal Sweeney	
	TL:	Bryan Riley	
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		N
	TL:		N
OSE/DMEPA (proprietary name)	Reviewer:	Alek Winiarski	Y
	TL:	Jamie Wilkins-Parker	N
OSE/DRISK (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Bioresearch Monitoring (OSI)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers	Biostatistics: Kareen Riviere		N
Other attendees	John Farley, Sumathi Nambiar		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☐ Not Applicable ☐ YES ☒ NO ☐ YES ☒ NO Requesting Bioequivalency Waiver
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed?	☐ YES Date if known:

Comments: ***If no, for an NME NDA or original BLA , include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: Yes.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review The draft package insert and container labels submitted in Section 1.14.1 describe the drug product as (b) (4) . In addition, the various sections of the labeling list (b) (4) s drug product components. However, the proposed drug product formulation provided in section 3.2.P.1 of Module 3 does not include these ingredients. Please resolve this discrepancy and submit a correct version of the draft container labels and package insert for the drug product.	☒ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☒ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Frances LeSane

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): N/A

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74

☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FARIBA IZADI
03/27/2014

FRANCES V LESANE
03/28/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 205572

Application Type: New Formulation

Name of Drug/Dosage Form: Moxifloxacin injection, solution (b) (4) 400 mg/250ml

Applicant: Fresenius Kabi USA

Receipt Date: June 06, 2013

Goal Date: April 07, 2014

1. Regulatory History and Applicant's Main Proposals

This NDA is for a new formulation, filed under the provision of 505(b)(2) for treating infections in adults ≥ 18 years of age caused by designated, susceptible bacteria.

Proposed Indication(s): Indicated for treating infections in adults ≥ 18 years of age caused by designated, susceptible bacteria:
Acute Bacterial Sinusitis
Acute Bacterial Exacerbation of Chronic Bronchitis
Community Acquired Pneumonia
Skin and Skin Structure Infections: Uncomplicated and Complicated
Complicated Intra-Abdominal Infections

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

The review of the prescribing information was reviewed and found to be acceptable.

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format

is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *The initial approval date will read June 20, 2014*

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

YES 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

NO 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

FARIBA IZADI
03/27/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 19, 2014

To: Fariba Izadi, Pharm.D., Regulatory Project Manager
Division of Anti-Infective Products (DAIP)

From: Christine Corser, Pharm.D., RAC, Regulatory Review Officer
Office of Prescription Drug Products (OPDP)

Subject: NDA 205572
Moxifloxacin Injection

OPDP acknowledges receipt of your consult request dated August 19, 2013, for the proposed labeling for Moxifloxacin Injection. Reference is made to a January 23, 2014, email from DAIP, which indicates that a Complete Response letter will be issued. For this reason, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DAIP submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Christine Corser at Christine.corser@fda.hhs.gov or (301) 796-2653.

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/s/

CHRISTINE G CORSER
02/19/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	February 10, 2014
To:	Sumathi Nambiar, MD Acting Director **Division of Anti-Infective Products (DAIP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Robin Duer, MBA, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Medication Guide (MG)
Drug Name (established name):	moxifloxacin hydrochloride injection
Dosage Form and Route:	solution (b) (4)
Application Type/Number:	NDA 205572
Applicant:	Fresenius Kabi USA, LLC

1 INTRODUCTION

On June 6, 2013, Fresenius Kabi USA, LLC submitted for the Agency's review a New Drug Application (NDA) for moxifloxacin hydrochloride injection, solution (b) (4) (b) (4) Moxifloxacin hydrochloride injection is a fluoroquinolone antibacterial indicated for treating infections in adults ≥ 18 years of age caused by designated, susceptible bacteria. The reference listed drug (RLD) for moxifloxacin hydrochloride injection is Avelox (moxifloxacin) hydrochloride injection, solution for IV use.

On October 1, 2013, the Division of Anti-Infective Products (DAIP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for for moxifloxacin hydrochloride injection.

This memorandum documents the DMPP review deferral of the Applicant's proposed MG for moxifloxacin hydrochloride injection.

2 CONCLUSIONS

Due to outstanding chemistry deficiencies, DAIP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

ROBIN E DUER
02/10/2014

MELISSA I HULETT
02/10/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	December 17, 2013
Reviewer:	Aleksander Winiarski, PharmD Division of Medication Error Prevention and Analysis
Acting Team Leader:	Morgan Walker, PharmD, MBA Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Moxifloxacin 400 mg/250 mL (b) (4)
Application Type/Number:	NDA 205572
Applicant/sponsor:	Fresenius Kabi
OSE RCM #:	2013-1820

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates container label, overwrap pouch labeling, Medication Guide and prescribing information for Moxifloxacin NDA 205572 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

NDA 205572 was submitted on June 6, 2013 and received on June 7, 2013. This is a 505B2 application. The Applicant plans to market the product without a proprietary name.

1.2 PRODUCT INFORMATION

The following product information was obtained from the proposed insert labeling, which was submitted on June 7, 2013:

- Active Ingredient: Moxifloxacin
- Indication of Use: Moxifloxacin injection is a fluoroquinolone antibacterial indicated for treating infections in adults ≥ 18 years of age caused by designated, susceptible bacteria for:
  - Acute Bacterial Sinusitis
  - Acute Bacterial Exacerbation of Chronic Bronchitis
  - Community Acquired Pneumonia
  - Skin and Skin Structure Infections: Uncomplicated and Complicated
  - Complicated Intra-Abdominal Infections
- Route of Administration: Intravenous
- Dosage Form: Injection solution
- Strength: 400 mg /250 mL infusion bag
- Dose and Frequency: Once every 24 hours
- How Supplied: Individual infusion bag in overwrap pouch
- Storage: Room Temperature

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for intravenous Moxifloxacin medication error reports (See Appendix A for a description of the FAERS database).

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date Searched	December 6, 2013 (no date ranges)
Drug Names	Moxifloxacin (product active ingredient)
MedDRA Search Strategy	Medication Errors HLGT Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified 151 cases. Each case was reviewed for relevancy and duplication. After individual review, 147 cases were not included in the final analysis for the following reasons: cases related to Moxifloxacin oral dosage forms, cases related to ophthalmic Moxifloxacin dosage forms, medication related to other suspect drug, adverse reaction unrelated to a medication error, and name confusion with the proprietary name Avelox. The remaining 4 cases are summarized in section 3.1 below.

2.2 LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label (Appendix B, image)
- Overwrap Labeling (Appendix C, image)
- Insert Labeling (no image)
- Medication Guide (no image)

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results and our risk assessment of Moxifloxacin intravenous labels and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, four Moxifloxacin intravenous injection medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2].

---

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

Wrong technique in drug co-administration (n=1)[3]

The case describes a patient who was prescribed both intravenous Furosemide and Moxifloxacin to be administered at approximately the same time. A precipitate in the line was witnessed by the nurse and pharmacist on the team. It was reported that the Furosemide had been infused in the same line immediately before the Moxifloxacin infusion was started. It is assumed that the line was not adequately flushed. The patient did not experience harm because the line was switched out and the Moxifloxacin dose was then infused without incident. Section 2.3 of the Avelox prescribing information clearly states to flush the line when infusing other products through the same line; therefore, the error is likely due to knowledge and/or performance deficits of the infusion nurse. No other patient outcomes were provided.

Potential wrong technique in drug administration (n=1)[4]

The case describes a nurse who reported potential problems with administration of intravenous Avelox by her staff. She reports that 6 patients in the previous 2 months have experienced redness of the arm following the outline of the vein. The patients did not confirm pain or itching. She stated that she was advised (reviewer comment: unclear by whom) to slow the infusion rate. She was aware that Avelox is supposed to be administered over 60 minutes. It is unclear from the case details if the rest of the staff were also aware that 60 minutes is the correct infusion time or if any of the cases may have resulted from miscalculation of the infusion rate. The root cause of the potential error was not specified and cannot be clearly determined from the limited information provided in the case. No other patient outcomes were provided.

Wrong technique in use error (n=2)[5]

Both cases describe users that have cut themselves on the foil overwrap or while handling the products (reviewer comment: although not specified it was likely on the foil overwrap in the second case). Foil overlaps are commonly used as part of the packaging of intravenous products. The root causes of the errors were not specified and cannot be clearly determined from the limited information provided in the cases. However since foil overwraps are commonly used with other intravenous bags the errors were likely due to inattention or knowledge deficits of the users. No other outcomes were provided.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The insert labeling clearly and prominently states that flushing of the line is required if Moxifloxacin is to be administered through the same line with other medications. Therefore, the wrong technique in drug co-administration error was likely associated with the user's knowledge and performance deficits. However, the proposed Moxifloxacin formulation differs in inactive ingredients and active drug salts from the approved Avelox formulation. Therefore, we cannot assume that this formulation will be compatible or

[3] Case 6057632 v1 Mfc number not listed, direct report

[4] Case 6119718 v1 Mfc number not listed, direct report

[5] Case 9145721 v1 Mfc US-BAYER-2013-023681 Case 9263761 v1 Mfc US-BAYER-2013-053900

incompatible with other medications or solutions as expressed in the Avelox insert and as described by secondary references, such as Trissel's Handbook on Injectable Drugs. Thus, we expressed concern to our ONDQA colleagues that the proposed Moxifloxacin product may be assumed to be the same as Avelox in terms of compatibility. In the absence of compatibility testing showing equivalent results between the formulations, this risk may be minimized with a non-interchangeable rating in the Orange Book, with an established name that differs in the salts, and potentially with additional language in the insert labeling and on carton and container labeling stating that the proposed formulation in not equivalent to Avelox. ONDQA stated that the current nomenclature for the proposed product is Moxifloxacin Injection, which is different from Moxifloxacin HCl on Avelox labels. Additionally, ONDQA has sent an information requests to the Applicant regarding additional compatibility studies and comparisons to the Avelox formulation.

The insert labeling also states that Moxifloxacin is to be administered over 60 minutes. It is unclear from the wrong technique in drug administration case if the staff ensured that the infusions were administered over 60 minutes. Also it's unclear from the case if the longer infusion time resulted in improved outcomes. However, to highlight that 60 minutes is the minimum time of infusion, DMEPA suggests a slight modification of the language such as: " … over at least 60 minutes", if considered appropriate by the Division.

We provide additional recommendations to improve communication of important information to minimize confusion and improve readability in sections 5.1 and 5.2 below.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label and labeling and to promote the safe use of the product.

5 RECOMMENDATIONS AND COMMENTS

5.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for the Division to consider implementing prior to approval of this NDA:

A. General

1. The submitted labels and labeling state that the established name for the product is Moxifloxacin HCl. Per our discussion with ONDQA the active pharmaceutical ingredient (b) (4) (b) (4) (b) (4) Therefore, please ensure that the Applicant revises all labels and labeling to reflect the correct established name, this revision will also help to differentiate this formulation from the currently approved intravenous Avelox.

B. Highlights of Prescribing Information and Full Prescribing Information, Dosage and Administration Sections

1. Revise the "IV" abbreviations to the word "intravenous", as the abbreviation "IV" has been identified on the Institutes for Safe Medications Practices (ISMP's) list of error-prone abbreviations[6].

2. If appropriate, consider adding the words "at least" or "a minimum of" to the infusion time statements. Similar to: "…over at least 60 minutes" or "…over a minimum of 60 minutes".

C. Medication Guide

1. See B1 (IV abbreviation in title) and B2 above.

2. The subsection "How should I store moxifloxacin" is inconsistent with section 16 of the full prescribing information. Since some patients may store this product at home for home infusion services and because refrigeration will result in precipitation we recommend adding correct storage information similar to: Store at room temperature, do not refrigerate, keep away from children. We defer to the patient labeling group and the Division for exact language.

5.2 COMMENTS TO THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Bag Label

1. Ensure that the presentation of the established name and statement of infusion time are consistent with the finalized insert labeling.

2. Ensure that the product name and strength statements are the most prominent information on the label by significantly increasing their size. Also ensure that the entire name, which includes the dosage form, appears in a single font size. Additionally, the NDC number competes for prominence with the name and strength statement, decrease the size of the NDC number and relocate it higher on the label, away from the name.

3. Increase the prominence of important storage information by increasing the size and bolding the statement "DO NOT REFRIGIRATE – PRODUCT PRECIPITATES UPON REFRIGIRATION'.

[6] http://www.ismp.org/tools/errorproneabbreviations.pdf, Accessed December 13, 2013.

4. To reduce clutter, ensure there is adequate empty space below the infusion time statement.

5. To improve readability, revise the text under the infusion time statement, from all capital letters to title case (as in the overwrap labeling and except for the "DO NOT REFRIGIRATE – PRODUCT PRECIPITATES UPON REFRIGIRATION" statement).

B. Overwrap Labeling

1. See A1 through A4 above.

If you have further questions or need clarifications, please contact Karen Townsend, OSE project manager, at 301-796-5413.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ALEKSANDER P WINIARSKI
12/17/2013

MORGAN A WALKER
12/17/2013