CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

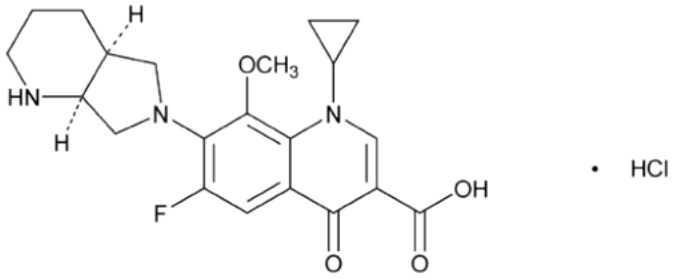
205572Orig1s000

CHEMISTRY REVIEW(S)

NDA 205-572

Moxifloxacin Injection, 400 mg/250 mL

Fresenius Kabi USA



Milton J. Sloan, Ph.D.
ONDP (ONDQA) Pre-Marketing Assessment Division I
Branch 3

For Division of Anti-Infective Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 205-572

2. REVIEW #: 2

3. REVIEW DATE: 28-Jan-2015; 10-Mar-2015

4. REVIEWER: Milton J. Sloan, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original (0000)	06-Jun-2013
Submission (0001)	25-Jun-2013
Submission (0002)	12-Nov-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Response to IR (0003)	10-Feb-2014
Resubmission (Incomplete) (0004)	29-Aug-2014
Resubmission (Class 2) (0005)	02-Oct-2014
Response to IR (0006)	09-Feb-2015
Response to IR (0007)	11-Feb-2015
Response to IR (0008)	20-Feb-2015
Response to IR (0010)	24-Mar-2015
Response to IR (0011)	25-Mar-2015
Response to IR (0012)	01-Apr-2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Fresenius Kabi USA, LLC
Address:	Three Corporate Drive Lake Zurich, IL 60047
Representative:	N/A
Telephone:	(847) 550-2300

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Moxifloxacin, Injection, 400 mg/250 mL,

b) Non-Proprietary Name (USAN): Moxifloxacin Injection, 400 mg/250mL

c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Sterile Injection

12. STRENGTH/POTENCY: 400mg/250mL (or 1.6g/mL)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X_ R_x ___OTC

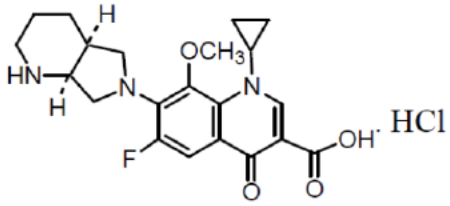
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Chemical name for moxifloxacin hydrochloride:

(b) (4)

CAS No. 186826-86-8
Structural formula:



Moxifloxacin hydrochloride has a molecular mass of 437.9 and a molecular formula of $C_{21}H_{(b)(4)}FN_3O_4 \cdot HCl$.

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

(b) (4)	II	(b) (4)	Moxifloxacin hydrochloride	1	Adequate	M. Farahani	Reviewed #10 (4/1/13) is adequate
26696	III	Fresenius Kabi Deutschland GmbH	**free***flex* ® Packaging System ((b) (4) Bag)		Adequate	Milton Sloan	Electronic DMF 26696 Reviewed #3 is Adequate with IR to Holder

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	021277	Avelox® I.V. (moxifloxacin HCl in NaCl injection)

18. STATUS:

ONDP:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	All Facilities Acceptable	04/02/2-15	Ruth Moore(see Attachment at end of Review)
Pharm/Tox	Approval	03/18/2015	Terry Miller, Ph. D.
Biopharm	Request for Bioequivalence waiver granted.	03/12/2015	Vidula R. Kolhatkar, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Not requested per ONDQA policy	N/A	N/A
DMEPA	Adequate	12/17/201	Jacqueline Sheppard
EA	Request for Categorical Exclusion-Acceptable	2/07/2014	Milton Sloan, Ph.D.
Quality Microbiology	Acceptable	2/07/2014	Neal Sweeney, P. D.

The Chemistry Review for NDA 205-572

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval. The Office of Compliance has made an overall acceptable recommendation for all facilities requested for inspection in the NDA.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Moxifloxacin hydrochloride anhydrous is a light yellow or yellow (b) (4), slightly hygroscopic. (b) (4) Please see Section 3.2.S (of the NDA and Review #1) for the complete details on the active pharmaceutical ingredient. The impurities in the drug substance are consistent with those specified on the USP monograph for moxifloxacin hydrochloride and drug substance manufacturer/supplier specifications. The drug substance is the anhydrous form as specified in the referenced DMF. The CMC information is referenced to DMF (b) (4) held by (b) (4) A letter of authorization (LOA) is included in the NDA submission. The DMF was previously reviewed and is adequate to support this NDA.

Drug Product

The proposed drug product is a new formulation of moxifloxacin hydrochloride injection solution. Moxifloxacin, Injection, 400 mg/250 mL, in **free***flex*® bags consists of moxifloxacin hydrochloride (b) (4) and inactive ingredients, sodium acetate trihydrate USP, disodium sulfate USP, sulfuric acid (NF), and water for injection (USP). All excipients used in the manufacture of FK USA's drug product meet the requirements of the current USP/NF.

The **free***flex*® container closure system for Moxifloxacin Injection consists of (b) (4) The 300 mL infusion bag is manufactured without (b) (4) latex or PVC

material. [redacted] The detailed composition of the components and component manufacturing methods are provided in the referenced type III DMF [redacted] DMF [redacted] filed with CBER.

Fresenius Kabi Norge (Norway) (FKN) manufactures, processes, labels, and package Moxifloxacin, Injection, 400 mg/250 mL, in a 300 mL capacity freeflex® bag. FKN also performs complete testing on the finished dosage form. The manufacturing process consists of [redacted] were reviewed by the Product Micro-Quality Reviewer, Dr. Neal Sweeney. The product quality microbiology review has no outstanding issues and recommends approval.

Bioequivalence

FK USA asserts that Moxifloxacin Injection was designed and developed to be therapeutically and functionally equivalent to Avelox®I.V. (moxifloxacin HCl in NaCl injection) marketed by Bayer and has requested a bioequivalence waiver. Excipients of FK USA's drug product differ from those contained in the reference listed drug (RLD) Avelox® I.V. (moxifloxacin HCl in NaCl injection). The recommended dose is equivalent to 0.4 g (400mg) of moxifloxacin free base. The excipients sodium acetate trihydrate (USP), disodium sulfate (USP) [redacted] and as tonicity modifiers [redacted] The target pH value [redacted] 5.0-6.0) of the solution differs with regard to the RLD (4.1-4.6). The biopharmaceutics reviewer has determined that the requested bioequivalence waiver for the proposed product be granted and approval is recommended (please see Dr. Vidula R. Kolhatkar review 3/12/2015). The amount of sodium renders FK USA's drug product not therapeutically equivalent and is addressed in the label.

B. Description of How the Drug Product is Intended to be Used

Moxifloxacin, Injection, 400 mg/250 mL, is a ready-to-use solution for infusion in **free***flex*® bags. Moxifloxacin, Injection is indicated for treatment of infections in adults caused by susceptible bacteria designated in the label. The dose of moxifloxacin injection is 400 mg once every 24 hours. The duration of therapy depends on the type of infection as described in label. The drug product is infused slowly over 60 minutes avoiding bolus. No other medication is to be mixed in the infusion bag or in I.V. line.

FK USA proposes the storage condition as recommended using USP controlled room storage statement "Store at 20-25°C (68-77°F). [(b) (4)] [see USP Controlled Room Temperature]. [(b) (4)]

FK USA has proposed a [(b) (4)] month expiration period based on the stability data of three pilot batches at 6 months accelerated (40 °C/≤ 25 % RH) and 24 months long-term (25 °C/40 % RH). Based on their proposed test attributes and acceptance criteria, the drug product remained relatively stable. The migration studies performed on same batches 12FCU92, 12FCU93, and 12FCU92 were updated and provide the concentration up to 24 months for the identified leachables. Based on the evaluation of the presented stability and migration data the recommended expiration period is for a [(b) (4)] months.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is recommended for approval. An overall acceptable recommendation on facilities inspection was made on April 02, 2015 (see Attachment). The recommended expiration period is [(b) (4)] months.

DMF [(b) (4)] referenced for the 300 mL **free***flex*® bag packaging system was deficient at the time of NDA submission and has since been amended. The extractable data for Type A primary film (SF9) was reviewed to support the 300 mL capacity bag for Moxifloxacin. The DMF [(b) (4)] was found adequate to support this NDA.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist: Milton J. Sloan, Ph.D. Date: 26-March-2015
Final 02-April-2015

Acting Branch Chief: Balajee Shanmugam, Ph.D. Date:

C. CC Block

Milton J. Sloan -S

Digitally signed by Milton J. Sloan -S
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Date: 2015.04.02 15:35:47 -04'00'

Balajee Shanmugam -S

Digitally signed by Balajee Shanmugam -S
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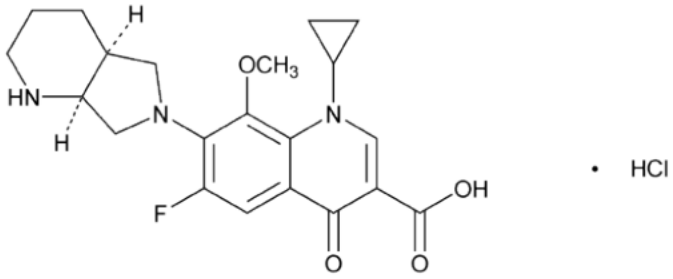
NDA 205-572

Moxifloxacin, Injection, 400 mg/250 mL

Fresenius Kabi USA



Milton J. Sloan, Ph.D.
ONDQA Pre-Marketing Assessment Division II Branch V

For Division of Anti-Infective Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 205-572

2. REVIEW #: 1

3. REVIEW DATE: 29-Jan-2014

4. REVIEWER: Milton J. Sloan, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	06-Jun-2013 25-Jun-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Fresenius Kabi USA, LLC
Address:	Three Corporate Drive Lake Zurich, IL 60047
Representative:	N/A
Telephone:	(847) 550-2300

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Moxifloxacin, Injection, 400 mg/250 mL,
b) Non-Proprietary Name (USAN): Moxifloxacin Injection, 400 mg/250mL
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Sterile Injection

12. STRENGTH/POTENCY: 400mg/250mL (or 1.6g/mL)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X_ R_x ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

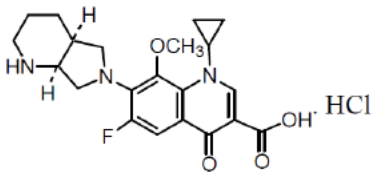
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name for moxifloxacin hydrochloride:

(b) (4)

CAS No. 186826-86-8

Structural formula:



Moxifloxacin hydrochloride has a molecular mass of 437.9 and a molecular formula of $C_{21}H_{(b)(4)}FN_3O_4 \cdot HCl$.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Moxifloxacin hydrochloride	1	Adequate	M. Farahani	Reviewed #10 (4/1/13) is adequate
26696	III	Fresenius Kabi Deutschland GmbH	**free***flex* ® Packaging System (Polyolefin Bag)		Inadequate	Electronic DMF	Inadequate IR sent from previous review: DMF (b) (4) filed BER (b) (4) DMF26696

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	021277	Avelox® I.V. (moxifloxacin HCl in NaCl injection)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Acceptable	6/29/2014	J. Williams
Pharm/Tox	Non Approval due to incomplete studies on container closure system	2/04/2014	Terry Miller, Ph. D.
Biopharm	Request for Bioequivalence waiver not granted.	1/27/2014	Kareen Riviere, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Not requested per ONDQA policy	N/A	N/A
DMEPA	Deficiencies with labeling	12/17/2014	Aleksander Winiarski, Pharm. D.
EA	Request for Categorical Exclusion-Acceptable	2/07/2014	Milton Sloan, Ph.D.
Quality Microbiology	Acceptable	2/07/2014	Neal Sweeney, P. D.

The Chemistry Review for NDA 205-572

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 205572 has not provided sufficient information to assure identity, strength, purity, and quality of the drug product and is not recommended for approval from Chemistry, Manufacturing, and Controls (CMC) perspective. CMC deficiencies are listed at the end of this review. The labeling is not finalized at this time. The Office of Compliance has made an Acceptable overall evaluation for the facilities (see Attachment). The final text of the deficiencies to be included in the CR letter will be captured in a separate memorandum placed in DARRTS.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Moxifloxacin hydrochloride anhydrous is a light yellow or yellow powder or crystals, slightly hygroscopic. It is (b) (4) Please see Section 3.2.S for the complete details on the active pharmaceutical ingredient. The impurities in the drug substance are consistent with those specified on the USP monograph for moxifloxacin hydrochloride and drug substance manufacturer/supplier specifications. The drug substance is the anhydrous form as specified in the referenced DMF. The CMC information is referenced to DMF (b) (4) held by (b) (4) A letter of authorization (LOA) is included in the NDA submission. The DMF was previously reviewed and is adequate to support this NDA.

Drug Product

The proposed drug product is a new formulation of moxifloxacin hydrochloride injection solution. Moxifloxacin, Injection, 400 mg/250 mL, in **free***flex*® bags consists of moxifloxacin hydrochloride (b) (4) and inactive ingredients, sodium acetate trihydrate USP, disodium sulfate USP, sulfuric acid (NF), and water for injection (USP). All excipients used in the manufacture of FK USA's drug product meet the requirements of the current USP/NF.

The **free***flex*® container closure system for Moxifloxacin Injection consists of (b) (4) The 300 mL infusion bag is manufactured without (b) (4) latex or PVC material. (b) (4) The detailed composition of the components and component manufacturing methods are provided in the referenced type III DMF (b) (4) DMF (b) (4) filed with CBER.

Fresenius Kabi Norge (Norway) (FKN) manufactures, processes, labels, and package Moxifloxacin, Injection, 400 mg/250 mL, in a 300 mL capacity **free***flex*® bag. FKN also performs complete testing on the finished dosage form. The manufacturing process consists of (b) (4) FK USA reports the (b) (4) (b) (4) are reviewed by the Product Micro-Quality Reviewer, Dr. Neal Sweeney. The product quality microbiology review has no outstanding issues and recommends approval.

Bioequivalence

FK USA asserts that Moxifloxacin Injection was designed and developed to be therapeutically and functionally equivalent to Avelox®I.V. (moxifloxacin HCl in NaCl injection) marketed by Bayer and has requested a bioequivalence waiver. Excipients of FK USA's drug product differ from those contained in the reference listed drug (RLD) Avelox® I.V. (moxifloxacin HCl in NaCl injection). The recommended dose is equivalent to 0.4 g (400mg) of moxifloxacin free base. The excipients sodium acetate trihydrate (USP), disodium sulfate (USP) (b) (4) as tonicity modifiers to maintain osmotic pressure close to isotonic. The target pH value (b) (4) of the solution differs with regard to the RLD (4.1-4.6). The biopharmaceutics wer has determined that the requested bioequivalence waiver for the proposed product cannot be granted at this time due to outstanding deficiencies.

B. Description of How the Drug Product is Intended to be Used

Moxifloxacin, Injection, 400 mg/250 mL, is a ready-to-use solution for infusion in **free***flex*® bags. Moxifloxacin, Injection is indicated for treatment of infections in adults caused by susceptible bacteria designated in the label. The dose of moxifloxacin injection is 400 mg once every 24 hours. The duration of therapy depends on the type of infection as described in label. The drug product is infused slowly over 60 minutes avoiding bolus. No other medication is to be mixed in the infusion bag or in I.V. line.

FK USA proposed a storage condition of [redacted] (b) (4) in NDA but does include in drug product labeling. Recommend using USP controlled room storage statement "Store at 20-25°C (68-77°F). [redacted] (b) (4) [see USP Controlled Room Temperature]. [redacted] (b) (4)

FK USA has proposed a [redacted] (b) (4) month expiration period based on the stability data of three pilot batches at 6 months accelerated (40 °C/≤ 25 % RH) and 12 months long-term (25 °C/40 % RH). Based on their proposed test attributes and acceptance criteria, the drug product remained relatively stable. No determination has been made on the proposed expiration period.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is not recommended for approval due to the following deficiencies listed below (see also List of Deficiencies Communicated at end of this review). The final text of the deficiencies that will be included in the CR letter will be captured in a separate memorandum placed in DARRTS.

The biopharmaceutics reviewer has determined that the requested bioequivalence waiver for the proposed product cannot be granted at this time due to outstanding deficiencies. Please refer to Dr. Kareen Riviere's review.

DMF [redacted] (b) (4) referenced for the 300 mL **free***flex*® bag packaging system was deficient at the time of NDA submission and remains deficient. A deficiency letter (June 2013) was sent to holder. The holder has not adequately amended the DMF to support this NDA.

The applicant has not established the safety of the observed leachables. For detailed discussion please refer to the Pharm-Tox review of Dr. Terry Miller. Additionally, the applicant's extractable assessment studies were not adequately designed to establish the maximum accumulation values of extractable and thereby the worst case potential to enable the safety evaluation/qualifications. Further, FK USA has not demonstrated adequate management of drug product leachables throughout the proposed shelf life.

The applicant failed to respond to Agency information requests sent in August and October, 2013 in a timely manner, and these are still outstanding. Therefore, the review team concluded that additional deficiencies identified will be included in the CR letter and will not communicated to the applicant during the review cycle. Please refer to the end of review for additional deficiencies.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist: Milton J. Sloan, Ph.D.	Date: 26-August-2013 Final Draft: 29-January-2014
Branch Chief: Rapti Madurawe, Ph.D.	Date:

C. CC Block

68 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MILTON J SLOAN
02/13/2014

RAPTI D MADURAWE
02/13/2014