CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205645Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dorota Matecka, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	205645
Applicant	Fresenius Kabi USA, LLC
Date of Submission	June 1, 2016 (*Class 2 NDA Resubmission*)
PDUFA Goal Date	December 1, 2016
Proprietary Name / Established (USAN) names	Tigecycline for Injection* (tigecycline)
Dosage forms/Strength	Powder for injection, 50 mg/vial
Proposed Indication(s)	Complicated skin and skin structure infections Complicated Intra-abdominal Infections Community-Acquired Bacterial Pneumonia
Recommended:	***Approval***

** No proprietary/trade name was proposed for the drug product*

1. Introduction

This 505(b)(2) NDA submitted by Fresenius Kabi, USA, LLC provides for a new injectable formulation of tigecycline to be used for the treatment of the same infections as listed in the listed drug labeling. The listed drug for this 505(b)(2) NDA is Tygacil ® (tigecycline) for Injection, 50 mg/vial, approved in 2005 via NDA 21821. The drug product proposed by Fresenius Kabi, USA, LLC, Tigecycline for Injection, 50 mg/vial, is a new formulation of tigecycline lyophilized powder for injection, and differs from the listed drug in the excipients used in the formulation; specifically, it contains a different (b) (4) (i.e., arginine instead of lactose). In view of the similarities between the proposed and reference listed drugs, a biowaiver for conducting in-vivo bioequivalence studies was requested by the Applicant. The Applicant is relying on previous findings of efficacy and safety for Tygacil® for approval of the proposed drug product.

This NDA, originally submitted on July 31, 2013, was issued a complete response (CR) letter on May 30, 2014 due to several Product Quality deficiencies. The CR issues were satisfactorily resolved via the first NDA resubmission submitted on May 29, 2015, and the NDA was tentatively approved on November 25, 2015 due to the pending patent issues. The current (second) NDA resubmission provides for few CMC changes related to Product Quality and no other changes have been proposed. Most of the reviewers found this NDA acceptable in the first review cycle, as described in their respective reviews of the original NDA and the previous CDTL reviews (dated May 22, 2014 and November 25, 2015). The current CTDL review covers only the changes proposed via current NDA resubmission, which include, as mentioned above, mainly CMC changes.

2. Background

Tigecycline is a tetracycline-class antibacterial drug. Tigecycline inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. Tigecycline is considered bacteriostatic; however, Tygacil has demonstrated bactericidal activity against isolates of *S. pneumoniae* and *L. pneumophila*. The antibacterial spectrum of tigecycline includes Gram-positive and Gram-negative organisms (including aerobic and anaerobic species), including methicillin-resistant *Staphylococcus aureus* (MRSA*), Legionella pneumophila*, and some Mycobacteria. Tigecycline is not active against *Pseudomonas aeruginosa* and has decreased activity against *Proteus*, *Providencia*, and *Morganella* species.

3. Product Quality

The CMC Reviewer of the current NDA resubmission was Yushi Feng, Ph.D.

The current NDA resubmission contains minor updates to the CMC sections; namely, the drug substance and drug product specifications have been updated to meet the USP monograph requirements (that became effective on December 01, 2015), and updated analytical procedures for assay and organic impurities for both drug substance and drug product, along with the respective validation reports, have also been provided. Dr. Feng found this information acceptable and recommended, based on previously reviewed compatibility data for this product, that (b) (4) (b) (4) be removed from the list of compatible drugs listed in the proposed package insert.

All manufacturing facilities have been found acceptable for this NDA and an acceptable Overall Recommendation was entered into Panorama by the Office of Process and Facilities on September 21, 2016. Based on the above findings, this NDA is recommended for approval from the Product Quality perspective (refer to the reviews dated November 8 and 23, 2016 in Panorama).

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Reviewer for the first NDA resubmission was Tessie Alapatt, Ph.D. who recommended this NDA for approval (refer to the review dated November 16, 2015 in DARRTS).

5. Clinical Pharmacology/Biopharmaceutics

Elsbeth Chikhale, Ph.D., was the Biopharmaceutics Reviewer and Zhixia (Grace) Yan, Ph.D., was the Clinical Pharmacology Reviewer for this application. They both recommended an

approval of this NDA in the first review cycle (refer to reviews dated March 12, 2014 and April 30, 2014, respectively, in DARRTS).

6. Clinical Microbiology

Kerian Grande Roche, Ph.D., was the Clinical Microbiology Reviewer for this application.

No new clinical microbiology information was submitted with this application. The Microbiology Reviewer recommended approval of this application from the microbiology standpoint with several recommended changes in the product package insert (refer to the review dated November 16, 2016 in DARRTS).

7. Clinical/Statistical

Dmitri Iarikov, MD, was the Clinical Reviewer, and Daniel Rubin, Ph.D., was the Statistical Reviewer for this NDA.

Dr. Iarikov recommended this application for approval in the first review cycle for the same indications as Tygacil® (refer to reviews dated April 30, 2014 and October 10, 2015 in DARRTS).

Dr. Rubin stated that no statistical review was needed for this application as there were no clinical studies submitted in this NDA (memorandum dated May 15, 2014 in DARRTS).

8. Safety

The Applicant of the current 505(b)(2) NDA is relying on the previous findings of safety for the listed drug, Tygacil® (tigecycline for injection). Tigecycline was found to be associated with an increase in all-cause mortality and the tigecycline package insert includes a boxed warning stating that "Tygacil should be reserved for use in situations when alternative treatments are not suitable." For details regarding safety assessment of tigecycline, refer to the reviews by Dr. Dmitri Iarikov (dated April 30, 2014 and October 10, 2015 in DARRTS).

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application (the product is not an NME).

10. Pediatrics

The drug product proposed via this 505(b)(2) NDA does not contain a new active ingredient and is not a new dosage form. No new indication is proposed and no new dosing regimen is proposed. There is no new route of administration associated with the new product. For these reasons, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), does not apply to this application. No pediatric studies will be required as a condition of approval.

11. Other Relevant Regulatory Issues

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI).

The reference listed application, NDA 21821 for Tygacil ® (tigecycline) for Injection, 50 mg/vial, has the following unexpired patents listed in the Orange Book:

- US Patent No. 7,879,828 - Expiry Date: February 5, 2029
- US Patent No. 8,372,995 - Expiry Date: October 8, 2030
- US Patent No. 8,975,242 - Expiry Date: October 24, 2028
- US Patent No. RE40183 - Expiry Date: April 9, 2016

In the initial NDA submission, Fresenius Kabi, USA, LLC submitted Paragraph III Certification for patent number RE40086 (*not listed above as it expired on June 25, 2013)* stating that "until all the above listed patent expire, FK USA will not distribute, for use or sale, Tigecycline for Injection (50 mg/vial), for which this 505(b)(2) New Drug Application is submitted." In addition, Fresenius Kabi, USA, LLC has submitted Paragraph IV Certification [per 21 CFR 314.50(i)(1)(i)(A)(4)] regarding the above patents (7,879,828; 8,372,995; and RE40183) stating that they are invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Tigecycline for Injection (50 mg/vial), for which this 505(b)(2) New Drug Application is submitted.

Subsequently, the applicant submitted an NDA amendment (dated November 27, 2013) in accordance with 21 CFR 314.95(b) to certify that notices regarding the "Paragraph IV" certification were delivered to the patent and the listed drug NDA holders: Fresenius Kabi, USA, LLC notified Pfizer, Inc., Wyeth LLC, and Wyeth Pharmaceuticals Inc. on October 2, 2013, and Wyeth Holding Corp. on October 3, 2013 [with the Fed Ex tracking receipts attached in the amendment]. The Applicant has notified the FDA via the same NDA Patent Amendment that on November 13, 2013, Pfizer Inc., Wyeth LLC, Pfizer Pharmaceuticals LLC, PF PRISM C.V, Pfizer Manufacturing Holdings LLC, Wyeth Holdings LLC, and Wyeth Holding Corporation have filed suit against Fresenius Kabi USA for patent infringement in the Unites States District Court for the District of Delaware (with a copy of Complaint attached in the amendment).

The NDA was further amended on October 28, 2015 with Revised Patent Certification (from Paragraph IV to Paragraph III Certification) for US Patent No. RE40183. In addition, Paragraph IV Certification was provided for US Patent No. 8,975,242 via a Patent Amendment dated November 20, 2015. A subsequent Patent Amendment was submitted by the Applicant

on November 25, 2015 to certify that notices regarding the “Paragraph IV” certification were delivered to the patent and the listed drug NDA holders.

In the NDA current resubmission, the Applicant notified the Agency that the court case regarding patents has been dismissed. The patent issues for this NDA have been reviewed by the 505(b)(2) review committee, which confirmed that the Applicant has provided all the necessary information and the patent matter has been now resolved (refer to the 505(b)(2) Assessment dated November 9, 2016 in DARRTS).

12. Labeling

The proposed labeling and labels for Tigecycline for Injection, 50 mg/vial, were submitted in the NDA. No trade name was proposed for the drug product.

Labeling revisions and recommendations were provided from all disciplines in the two previous review cycles. Several additional recommendations for the container and carton labels were provided by the DMEPA Reviewer, Deborah Myers, RPh, MBA (via reviews dated November 15 and November 18, 2016, in DARRTS). All recommended labeling revisions were incorporated in the package insert and vial and carton labels.

13. Recommendations/Risk Benefit Assessment

I concur with the assessments made by the review team and recommend this NDA for approval.

Dorota M. Matecka -S

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Date: 2016.12.01 09:02:02 05'00'

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dorota Matecka, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	205645
Applicant	Fresenius Kabi USA, LLC
Date of Submission	May 29, 2015 (*Class 2 NDA Resubmission*)
PDUFA Goal Date	November 29, 2015
Proprietary Name / Established (USAN) names	Tigecycline for Injection* (tigecycline)
Dosage forms/Strength	Powder for injection, 50 mg/vial
Proposed Indication(s)	Complicated skin and skin structure infections Complicated Intra-abdominal Infections Community-Acquired Bacterial Pneumonia
Recommended:	***Tentative Approval***

** No proprietary/trade name was proposed for the drug product*

1. Introduction

This 505(b)(2) NDA submitted by Fresenius Kabi, USA, LLC provides for a new injectable formulation of tigecycline to be used for the treatment of the same infections as listed in the listed drug labeling. The listed drug for this 505(b)(2) NDA is Tygacil ® (tigecycline) for Injection, 50 mg/vial, approved in 2005 via NDA 21821. The drug product proposed by Fresenius Kabi, USA, LLC, Tigecycline for Injection, 50 mg/vial, is a new formulation of tigecycline lyophilized powder for injection, and differs from the listed drug in the excipients used in the formulation; specifically, it contains a different (b) (4) (i.e., arginine instead of lactose).

No clinical data have been submitted in this NDA as the Applicant is relying on previous findings of efficacy and safety for Tygacil® for approval of the proposed drug product. The majority of the information submitted in the NDA relates to the chemistry, manufacturing and controls used in the manufacture of the proposed tigecycline drug product. In view of the similarities between the proposed and listed drugs, a biowaiver for conducting in-vivo bioequivalence studies was requested by the applicant on the basis of 21 CFR 320.22 (b): "a drug product's in vivo bioavailability or bioequivalence may be considered self-evident".

This NDA, originally submitted on July 31, 2013, was issued a complete response (CR) letter on May 30, 2014 and cited several Product Quality deficiencies including the deficiencies related to the drug product manufacturing facility, Fresenius Kabi USA, LLC, Grand Island, NY. Most of the reviewers found this NDA acceptable in the first review cycle as described in their respective reviews of the original NDA and the first CDTL review dated May 22, 2014. The current CTDL review covers only the reviews of the Applicant's response to the deficiencies outlined in the CR letter.

2. Background

Tigecycline is a tetracycline-class antibacterial drug. Tigecycline inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. Tigecycline is considered bacteriostatic; however, Tygacil has demonstrated bactericidal activity against isolates of *S. pneumoniae* and *L. pneumophila*. The antibacterial spectrum of tigecycline includes Gram-positive and Gram-negative organisms (including aerobic and anaerobic species), including methicillin-resistant *Staphylococcus aureus* (MRSA*), Legionella pneumophila*, and some Mycobacteria. Tigecycline is not active against *Pseudomonas aeruginosa* and has decreased activity against *Proteus, Providencia*, and *Morganella* species.

Tygacil ® (tigecycline) for Injection, 50 mg/vial, was approved via NDA 21821 in 2005. There are no other tigecycline formulations approved for use in humans in the US at this time. As discussed above, the drug product proposed by Fresenius Kabi, USA, LLC has the same drug substance, dosage form, concentration, route of administration, and indications as Tygacil®. Due to the difference in the formulation (i.e., a change in the excipients not permitted per 314.94(a)(9)(iii)), this application was submitted as 505(b)(2) application and not as a 505(j) application.

3. CMC/Product Quality Microbiology

The Product Quality Microbiology Reviewer was Vinayak B. Pawar, Ph.D. who recommended this NDA for approval from the product quality microbiology standpoint in the first review cycle (review dated January 27, 2014 in DARRTS). Since no updated product quality information was provided in the resubmission, Dr. Pawar continues to recommend this NDA for approval from microbiology product quality standpoint based on the information provided in the original submission (review in DARRTS, dated October 16, 2015).

The CMC Reviewer of the original NDA was Maotang Zhou, Ph.D., who recommended a non-approval based on several outstanding product quality deficiencies including the deficiencies related to the drug product manufacturing facility, Fresenius Kabi USA, LLC facility in Grand Island, NY, which was under an OAI alert.

The CMC Reviewer of the NDA resubmission was Yushi Feng, Ph.D. who concluded that the Product Quality deficiencies listed in the CR letter for the original NDA have been resolved satisfactorily. All manufacturing facilities including the drug product facility, Fresenius Kabi USA, LLC facility in Grand Island, NY have been found acceptable for this NDA and an acceptable Overall Manufacturing Inspection Recommendation was entered into Panorama by the Office of Process and Facilities. The (b) (4) impurity was not found to be mutagenic as confirmed by Dr. Tessie Alapatt who was the Pharmacology/Toxicology Reviewer for this NDA resubmission. The acceptable data were provided to demonstrate compatibility of the

proposed drug product with several other drugs listed in the package insert, except for haloperidol. In addition, data were not provided to support compatibility of the proposed drug product with (b) (4) (b) (4) therefore, these two drugs will not be included in the list of compatible drugs in Section 2.4 of the proposed package insert and haloperidol will be included in the list of incompatible drugs. Also, in response to the additional Product Quality comment included in the CR letter, adequate extractable/leachable information was provided in the resubmission for the proposed drug product container closure, (b) (4) rubber stopper.

Based on the above findings, this NDA is now recommended for approval from the Product Quality perspective (refer to the review by Yushi Feng, Ph.D., dated November 19, 2015 in Panorama).

4. Nonclinical Pharmacology/Toxicology

Dr. Wendy Schmidt was the Pharmacology/Toxicology Reviewer of the original NDA submission and concluded that from the nonclinical pharmacology standpoint, the NDA can be approved (for details refer to the review dated September 26, 2013 in DARRTS).

The Pharmacology/Toxicology Reviewer for the NDA resubmission was Tessie Alapatt, Ph.D. The Applicant has not performed any new nonclinical toxicology, genotoxicity, carcinogenicity, reproductive toxicity, or special toxicity studies with the drug product in support of this application. In addition, no nonclinical toxicology studies for tigecycline were identified in the literature. The only new nonclinical study report submitted and reviewed by Dr. Alapatt in this review cycle was a genotoxicity study (Ames assay) for the process impurity called (b) (4). Dr. Alapatt concurred with the Applicant's findings that the (b) (4) impurity was not found to be mutagenic. Therefore, Dr. Alapatt recommended this NDA for approval (refer to the review dated November 16, 205 in DARRTS).

5. Clinical Pharmacology/Biopharmaceutics

Elsbeth Chikhale, Ph.D., was the Biopharmaceutics Reviewer and Zhixia (Grace) Yan, Ph.D., was the Clinical Pharmacology Reviewer for this application. They both recommended an approval of this NDA in the first review cycle (refer to reviews dated March 12, 2014 and April 30, 2014, respectively, in DARRTS). No new reviews were conducted for this NDA resubmission.

6. Clinical Microbiology

Kerian Grande Roche, Ph.D., was the Clinical Microbiology Reviewer for this application.

No new clinical microbiology information was submitted with this application. The Microbiology Reviewer recommended approval of this application from the microbiology

standpoint with several recommended changes in the product package insert (refer to the review dated November 2, 205 in DARRTS).

7. Clinical/Statistical - Efficacy

Dmitri Iarikov, MD, was the Clinical Reviewer, and Daniel Rubin, Ph.D., was the Statistical Reviewer for this NDA.

Dr. Iarikov recommended this application for approval in the first review cycle (review dated April 30, 2014 in DARRTS) for the same indications as Tygacil® noting that tigecycline represents a viable treatment option for approved indications in situations when alternative treatments are not suitable for reasons related to allergies, microbial resistance, renal impairment or other circumstances that may preclude the use of other antibacterial drugs. As no additional clinical information has been provided in the NDA resubmission, Dr. Iarikov continues to recommend this application for approval from the clinical reviewer perspective based on the information provided in the initial submission (refer to review dated October 10, 2015 in DARRTS).

Dr. Rubin stated that no statistical review was needed for this application as there were no clinical studies submitted in this NDA (memorandum dated May 15, 2014 in DARRTS). No new review was filed for the NDA resubmission.

8. Safety

The applicant of the current 505(b)(2) NDA is relying on the previous findings of safety for the listed drug, Tygacil® (tigecycline for injection). Tigecycline was found to be associated with an increase in all-cause mortality and the tigecycline package insert includes a boxed warning stating that "Tygacil should be reserved for use in situations when alternative treatments are not suitable." For details regarding safety assessment of tigecycline, refer to the reviews by Dr. Dmitri Iarikov (dated April 30, 2014 and October 10, 2015 in DARRTS).

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application (the product is not an NME).

10. Pediatrics

The drug product proposed via this 505(b)(2) NDA does not contain a new active ingredient and is not a new dosage form. No new indication is proposed and no new dosing regimen is proposed. There is no new route of administration associated with the new product. For these reasons, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), does not apply to this application. No pediatric studies will be required as a condition of approval.

11. Other Relevant Regulatory Issues

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI).

The reference listed application, NDA 21821 for Tygacil ® (tigecycline) for Injection, 50 mg/via, has the following unexpired patents listed in the Orange Book:

- US Patent No. 7,879,828 - Expiry Date: February 5, 2029
- US Patent No. 8,372,995 - Expiry Date: October 8, 2030
- US Patent No. 8,975,242 - Expiry Date: October 24, 2028
- US Patent No. RE40183 - Expiry Date: April 9, 2016

In the initial NDA submission, Fresenius Kabi, USA, LLC submitted Paragraph III Certification for patent number RE40086 (*not listed above as expiring on June 25, 2013)* stating that "until all the above listed patent expire, FK USA will not distribute, for use or sale, Tigecycline for Injection (50 mg/vial), for which this 505(b)(2) New Drug Application is submitted." In addition, Fresenius Kabi, USA, LLC has submitted Paragraph IV Certification [per 21 CFR 314.50(i)(1)(i)(A)(4)] regarding the above patents (7,879,828; 8,372,995; and RE40183) stating that they are invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Tigecycline for Injection (50 mg/vial), for which this 505(b)(2) New Drug Application is submitted.

Subsequently, the applicant submitted an NDA amendment (dated November 27, 2013) in accordance with 21 CFR 314.95(b) to certify that notices regarding the "Paragraph IV" certification were delivered to the patent and the listed drug NDA holders: Fresenius Kabi, USA, LLC notified Pfizer, Inc., Wyeth LLC, and Wyeth Pharmaceuticals Inc. on October 2, 2013, and Wyeth Holding Corp. on October 3, 2013 [with the Fed Ex tracking receipts attached in the amendment]. The Applicant has notified the FDA via the same NDA Patent Amendment that on November 13, 2013, Pfizer Inc., Wyeth LLC, Pfizer Pharmaceuticals LLC, PF PRISM C.V, Pfizer Manufacturing Holdings LLC, Wyeth Holdings LLC, and Wyeth Holding Corporation have filed suit against Fresenius Kabi USA for patent infringement in the Unites States District Court for the District of Delaware (with a copy of Complaint attached in the amendment).

The NDA was further amended on October 28, 2015 with Revised Patent Certification (from Paragraph IV to Paragraph III Certification) for US Patent No. RE40183. In addition, Paragraph IV Certification was provided for US Patent No. 8,975,242 via a Patent Amendment dated November 20, 2015. A subsequent Patent Amendment was submitted by the Applicant on November 25, 2015 to certify that notices regarding the "Paragraph IV" certification were delivered to the patent and the listed drug NDAholders.

12. Labeling

The proposed labeling and labels for Tigecycline for Injection, 50 mg/vial, were submitted in the NDA. No trade name was proposed for the drug product.

Labeling revisions and recommendations were provided from all disciplines including OPDP (review by Adam George, Pharm.D. dated October 21, 2015 in DARRTS) and DMEPA (reviews by Jacqueline Sheppard, Pharm.D., dated August 5 and October, 2015). All recommended labeling revisions were incorporated in the package insert and vial and carton labels.

13. Recommendations/Risk Benefit Assessment

I concur with the assessments made by the review team and recommend the issuance of an approval for this NDA. However, due to the pending patent issues for Tygacil®, a tentative approval is recommended at the present time.

Dorota M. Matecka -S