CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205645Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205645 SUPPL # HFD # 520

Trade Name Tigecycline Injection

Generic Name tigecycline injection

Applicant Name Fresenius Kabi, USA, LLC

Approval Date, If Known December 1, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

As stated in the Biopharmaceutics review dated March 12, 2014

According to CFR 320.22(b), for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement for the submission of in vivo BA/BE data of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following:

- Is a parenteral solution intended solely for administration by injection, and

- Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

The only difference between the proposed drug product and the listed drug (Tygacil®) is the presence of (b) (4) mg L-arginine in the proposed product instead of the presence of 100 mg lactose monohydrate in the listed drug, Tygacil®. The Applicant has provided calculations indicating that the proposed dosing regimen would result in a maximum daily administration of <250 mg L-arginine from the proposed formulation in a single day, suggesting that the doseadministered would be significantly less than the L-arginine dose consumed on a typical day from the diet. The Applicant has also provided a summary of their literature search indicating that the significant difference between the pharmacologically active L-arginine dose (6 g iv) and that expected from the proposed product suggests that the dose of L-arginine administered from the proposed product would be too low to significantly alter hemodynamics or elimination of tigecycline. Therefore, the Applicant claims that it can be assumed that the substitution of Larginine for lactose monohydrate would not be expected to alter systemic exposure to tigecycline, due to altered hemodynamics or renal function.

The Applicant provided adequate information demonstrating that the differences in the proposed formulation vs. the listed drug did not affect the osmolality or the pH of the proposed drug product, once it is diluted to at least 1 mg/mL. In addition, the Applicant provided a summary of literature search showing that the dose of L-arginine from the proposed product would be very low to significantly alter the hemodynamics or elimination of tigecycline. In conclusion, considering the fact that tigecycline has a good solubility in water together with the overall information for the pH, osmolality, and pharmacological activity of L-arginine, there is adequate scientific evidence supporting the approval of the in vivo BA/BE waiver request for the proposed tigecycline for injection administered by the IV route, and therefore the Applicant's Biowaiver request for their proposed tigecycline for injection product administered by the IV route is acceptable and the Biowaiver is granted.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☐

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved

the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical

investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

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Name of person completing form: Carmen DeBellas, PharmD, RPh
Title: Regulatory Project Manager
Date: January 2, 2017

Name of Division Director signing form: Sumathi Nambiar, MD, MPH
Title: Director
Division of Anti-Infective Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

CARMEN L DEBELLAS
01/02/2017

SUMATHI NAMBIAR
01/03/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205645	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: tigecycline for injection 50 mg/vial Established/Proper Name: none Dosage Form: Injection		Applicant: Fresenius Kabi USA
RPM: Carmen DeBellas		Division: Division Anti-Infective Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: November 30, 2016

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action Complete Response • User Fee Goal Date is December 1, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	Complete Response May 30, 2014 Tentative Approval November 25, 2015
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received ☒ N/A
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 5S
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Complete Response May 30, 2014; Tentative Approval November 25, 2015; Approval December 1, 2016
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included Re-Submission June 1, 2016; and original label November 8, 2013
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included N/A
• Original applicant-proposed labeling	☐ Included N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	None None
❖ Labeling reviews *(indicate dates of reviews)*	RPM: March 27, 2014 DMEPA: November 18, 2016 November 15, 2016 October 8, 2015 August 3, 2015 March 20, 2014 DMPP/PLT (DRISK): ☒ None OPDP: October 21, 2015 SEALD: ☒ None CSS: ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	Filing Review January 21,2014 April 29, 2014
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	No clinical trials were performed

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: The innovator product was released from the pediatric study requirement because of a mortality issue.	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)*	Information Request Letters-July 2016; May 1, 2014; January 24, 2014 & December 3, 2013 Email Information Requests October 18, 2016; August 6, 2015; June 30, 2015; June 14, 2014; April 22, 2014; April 14, 2014; March 21, 2014, & March 14, 2014
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ December 1, 2016; November 25, 2015 & May 30, 2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ December 1, 2016; November 25, 2015 & May 22, 2014
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	October 20, 2015 & April 30, 2014

• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	505(b)(2) with no clinical studies
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A N/A ☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ November 16, 2016 November 2, 2015 April 28, 2014
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☒ Memo dated May 15, 2014
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ November 25, 2015 & April 30, 2014
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ September 26, 2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☒ Memo- November 22, 2016 Reviews- December 1, 2016; November 19, 2015; May 30, 2014 & April 25, 2014 Biopharmaceutics March 12, 2014
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ October 16, 2015 & January 27, 2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	April 25, 2014 See CMC review
☐ Review & FONSI *(indicate date of review)*	N/A
☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: April 25, 2014 See CMC Review pages 81-87 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be wit hin **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☐ Done

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205645

INFORMATION REQUEST

Fresenius Kabi USA, LLC
Attention: Kurt Pearl, MChE, Regulatory Specialist
Three Corporate Drive
Lake Zurich, IL 60047

Dear Mr. Pearl:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tigecycline for Injection.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response, by October 25, 2016, in order to continue our evaluation of your NDA.

1. The analytical procedures validation protocol for the drug substance impurities method, the acceptance criteria for the %RSD of precision (b) (4) were set at as high as (b) (4)%. The %RSD results for are as high as (b) (4)%. Explain the rationale for setting such high acceptance criteria and the results.

2. We note that (b) (4) was not tested in the compatibility study submitted previously (supporting document number 13, eCTD Sequence Number 0011, submit date 05/29/2015). As a result, as presented in the package insert in the tentative approval letter dated 25 Nov 2015, (b) (4) remove (b) (4) from the list of compatible drugs.

If you have any questions, call Navdeep Bhandari, Regulatory Business Process Manager, at (240) 402 -3815.

Sincerely,

LT Navi Bhandari, Pharm.D, USPHS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality

From: DeBellas, Carmen
Sent: Tuesday, October 18, 2016 10:41 AM
To: kurt.pearl@fresenius-kabi.com
Subject: NDA 205645 Patent Information Needed

Hi Kurt,

Thank you for the updated label. We received the submission yesterday.

Our 505(b)(2) review group has reminded me that the innovator has listed a new patent that you
will need to address:

Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or
statement (stating that a method of use patent does not claim a use for which the applicant is
seeking approval) with respect to any relevant patents that claim the listed drug or that claim any
other drugs on which investigations relied on by the applicant for approval of the application were
conducted, or that claim a use for the listed or other drug. Your 505(b)(2) application relies upon
the Agency's finding of safety and effectiveness for Tygacil (NDA 21821), but does not contain an
appropriate patent certification with respect to each patent listed in FDA's "Approved Drug
Products with Therapeutic Equivalence Evaluation" (the Orange Book) for the listed drug. For
Tygacil (NDA 21821), the Orange Book currently lists unexpired patent, 9254328. You must
provide an appropriate patent certification for the unexpired patent and indicate to which patent the
certification pertains by including the relevant patent number in the certification statement.

Thanks,

Carmen

Carmen DeBellas, PharmD, RPh
Chief Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
10/18/2016

From: DeBellas, Carmen
Sent: Thursday, August 06, 2015 8:19 AM
To: 'kurt.pearl@fresenius-kabi.com'; 'jeremy.rybicki@fresenius-kabi.com'
Subject: NDA 205645 Carton and Container label review comments

Good morning,

Please find review comments for your response to our original carton and container comments.

A. All Container Labels and Carton Labeling

1. Ensure the container and tray package have different National Drug Code (NDC) numbers to reflect the difference between the packaging size for the single vial versus the 10 vial per tray package configurations to minimize the risk for selecting the wrong package size. Revise the presentation of the NDC similar to ((b) (4) and 63323-960-10).

Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
08/06/2015

From: DeBellas, Carmen
Sent: Tuesday, June 30, 2015 9:00 AM
To: 'kurt.pearl@fresenius-kabi.com'; 'jeremy.rybicki@fresenius-kabi.com'
Subject: NDA 205645 information request (cmc/pharm-tox)

Good morning,

The Division has another information request for your resubmission for tigecycline injection. Can you respond as quickly as possible with this request.

"In order to determine the qualification of impurity (b) (4) in tigecycline, the complete study report of the Ames assay (summary submitted in the March 21, 2014 response to the FDA) must be submitted. If it is already in the submission, please direct us to its location."

Also, Can you provide an update of status of the law suit filed last year?

Thank you,

Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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CARMEN L DEBELLAS
06/30/2015

From: DeBellas, Carmen
Sent: Wednesday, June 24, 2015 2:23 PM
To: 'kurt.pearl@fresenius-kabi.com'
Subject: NDA 205645 tigecycline information request

Hello,

Please provide 2 product samples in the proposed commercial container closure system.

Send them to the following address:
FDA/CDER/OND/OAP/DAIP
Carmen DeBellas
10903 New Hampshire Avenue
Building #22 Room 6232
Silver Spring, MD 20903

Thank you,

Carmen DeBellas

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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CARMEN L DEBELLAS
06/24/2015

From: Bhandari, Navdeep
To: "Jeremy.Rybicki@fresenius-kabi.com"
Subject: RE: NDA 205645 (tigecycline) IR
Date: Wednesday, May 14, 2014 6:55:00 AM
Importance: High

Good Morning Jeremy,

Please see the following comments from my team regarding clarifications to our IR (dated May 1, 2014):

1. The purpose of the extractable/leachable studies is to demonstrate the compatibility of the proposed stopper with the proposed drug product. Therefore, we recommend you conduct a one-time extractable/leachable investigation that should include 1) extraction studies (to identify potential leachables), and 2) testing for leachables performed on 1-3 drug product batches (reconstituted product) stored at room temperature for a minimum of 24 hours (vials placed in upright and inverted positions). An appropriate control sample should be used. The resulting samples should be analyzed by appropriate screening techniques such as GC an HPLC, in combination with any detection techniques (i.e., Mass Spectrometry) that are capable of identifying the structure of extractable/leachable.

2. The paragraph entitled "Compatibilities" in Section 2.4 of the proposed package insert clearly indicates that tigecycline for injection can be administered simultaneously with different drugs through the y-site. Therefore, we recommend that you submit the requested supporting data for each listed drug.

Thank you,
Navi

From: Jeremy.Rybicki@fresenius-kabi.com [mailto:Jeremy.Rybicki@fresenius-kabi.com]
Sent: Friday, May 02, 2014 11:26 AM
To: Bhandari, Navdeep
Subject: RE: NDA 205645 (tigecycline) IR

Hi Navi,

The package insert states that there is a 6 hour room temp limit for the reconstituted solution and therefore the question is around the need for the extractable & leachable study for reconstituted solutions for that time period. The second question is for the need for the drug compatibility study when the other drugs are administered via a y-site and the package insert states to flush the line after administration.

Are these questions best discussed over the telephone or can the team provide more input on the need for the two requests via email?

Sincerely,
Jeremy
Jeremy Rybicki

Manager, I&D Regulatory Affairs

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, Illinois 60047
T: +1 847.550.2227
F: +1 847-550-7120
C: (b) (6)
Jeremy.Rybicki@fresenius-kabi.com
www.fresenius-kabi.us

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/s/

NAVDEEP BHANDARI
05/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205645

INFORMATION REQUEST

Fresenius Kabi USA, LLC
Attention: Jeremy Rybicki
Manager Regulatory Affairs
Three Corporate Drive
Lake Zurich, IL 60047

Dear Mr. Rybicki:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tigecycline for Injection, 50 mg/vial.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response, in order to continue our evaluation of your NDA.

1. In Section 2.4 of the proposed package insert, the drug product is stated to be compatible with several other drugs. To support this statement, for each drug listed, provide physical and chemical compatibility data with your drug product. This should include tests for appearance, description (color, visible particulates, turbidity), sub-visible particulates (i.e., USP <788> compliance), and assay, at a minimum.

2. Please provide results of the extractable and leachable studies for the proposed (b) (4) rubber stopper using suitable solvents and the reconstituted solutions of the proposed drug product, tigecycline for injection, with the proposed reconstitution diluents.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 -3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWE
05/01/2014

From: DeBellas, Carmen
Sent: Tuesday, April 22, 2014 3:30 PM
To: jeremy.rybicki@fresenius-kabi.com
Subject: NDA 205645 additional carton and container comments

Hello Jeremy,

The Agency has a few more comments for your carton and container labels below:

1. Please add the following information to the proposed carton label:
    a. Lot number and expiration date
    b. A statement of being sterile
2. Please add the following information to the proposed immediate container label:
    a. Storage conditions
    b. A statement of being sterile

Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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CARMEN L DEBELLAS
04/22/2014

From:	Bhandari, Navdeep
To:	"jeremy.rybicki@fresenius-kabi.com"
Subject:	NDA 205645 (tigecycline) IR Quick Turnaround Requested
Date:	Monday, April 14, 2014 10:11:00 AM
Importance:	High

Hello Jeremy,

Please provide a response to the following comment by my team within 24 hours.

"The drug substance establishments provided to-date in your NDA 205645 are inconsistent with those provided in DMF (b) (4). Amend the drug substance establishment information in the NDA with a complete and accurate list of ALL facilities involved in the manufacture and testing of the drug substance. Include all necessary information for each establishment such as contact name(s), address, phone number, fax number, and email addresses."

Please confirm receipt of this email.

Thank you,

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/CDER/FDA
240-402-3815

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/s/

NAVDEEP BHANDARI
04/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205645

DISCIPLINE REVIEW LETTER

Fresenius Kabi USA, LLC
Attention: Wanda Freeman-Sewell
Regulatory Specialist, CMC
Three Corporate Drive
Lake Zurich, IL 60047

Dear Ms. Freeman-Sewell:

Please refer to your July 31, 2013, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tigecycline For Injection, 50 mg/vial.

Our review of the Chemistry Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

Reference is made to your communication dated February 27, 2014 containing a response to FDA's CMC Information Request letter dated December 3, 2013. We have reviewed your response to Question 6(b) concerning the suitability of the analytical method for the (b) (4) impurity and find your response inadequate. (b) (4), it appears unlikely you are able to quantify this particular impurity accurately with the current HPLC method. Although you stated that (b) (4) is a process impurity as well as a degradation product, this impurity was not included in Table 3.2.P.5.5-1. In order to continue evaluation of the (b) (4) impurity, we request a written response to the following deficiencies on or before April 4, 2014.

1. The (b) (4) impurity contains a structural alert for mutagenicity. Evaluate the mutagenic potential of (b) (4)

2. How did you determine that (b) (4) is a degradation product? Provide supporting data.

3. Propose a possible mechanism for the formation of (b) (4) as a degradation product.

4. Develop an appropriate analytical procedure that is capable of accurately quantitating (b) (4) levels and provide representative batch analysis data for the (b) (4) impurity using this method. Note that the appropriate limit of detection and limit of quantitation for the (b) (4) analytical method would be based on the outcome of item #1 above.

5. If (b) (4) is confirmed to be mutagenic, provide an appropriate control strategy for (b) (4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWE
03/21/2014

From: DeBellas, Carmen
Sent: Friday, March 21, 2014 10:09 AM
To: wanda.freemansewell@fresenius-kabi.com
Subject: NDA 205645- tigecycline labeling information request

Hello Ms. Freeman- Sewell;

Please find attached Agency recommendations for your carton and container labels for NDA 205645. Kindly review the labeling recommendation and if you agree amend the NDA with update carton and container labels.

Thank you,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

The Agency recommends the following revisions prior to the approval of the NDA:

A. Vial Labels

1. The Principal Display Panel (PDP) contains the I.V. abbreviation, which is listed on Institute for Safe Medication Practices' (ISMP) list of error-prone abbreviations1. Replace the I.V. abbreviation with the word "Intravenous" for clarity.

2. For consistency with the insert labeling, revise the statement [redacted] (b) (4) to "Single Dose Vial" and relocate it to appear directly under the "For Intravenous Infusion Only" statement for increased prominence.

3. To improve prominence of important use information, relocate the statement "Discard Unused Portion" from the side panel to under the "Single Dose Vial" statement.

4. The statement "Not Made with Natural Rubber Latex" is important use information; therefore, please add the statement to the side panel.

5. To improve readability, revise the letter case of the established name "TIGECYCLINE FOR INEJCTION" from all capitals to title case to read "Tigecycline for Injection".

B. Carton Labeling

1. See A1, A2, A3 and A5 above.

2. To improve readability revise the letter case of the statement [redacted] (b) (4) from allcapitals to title case to read: [redacted] (b) (4)

3. Currently, the Usual Dosage statement [redacted] (b) (4) provides one of the recommended dosage regimens. To help ensure correct dosing, revise the Usual Dosage statement to read "Dosage and Administration: See package insert".

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/s/

CARMEN L DEBELLAS
03/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205645

INFORMATION REQUEST

Fresenius Kabi USA, LLC
Attention: Wanda Freeman-Sewell
Regulatory Specialist, CMC
Three Corporate Drive
Lake Zurich, IL 60047

Dear Ms. Freeman-Sewell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tigecycline for Injection, 50 mg/vial.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by February 5, 2014, in order to continue our evaluation of your NDA.

1. Provide comparative pH and osmolality data on your proposed drug product and the listed drug.

    - Justify any observed differences.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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RAPTI D MADURAWE
01/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205645

INFORMATION REQUEST

Fresenius Kabi USA, LLC
Attention: Wanda Freeman-Sewell
Regulatory Specialist, CMC
Three Corporate Drive
Lake Zurich, IL 60047

Dear Ms. Freeman-Sewell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tigecycline for Injection, 50 mg/vial.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by December 23, 2013, in order to continue our evaluation of your NDA.

1. In reference to Section 3.2.S.4.1 of the NDA submission concerning the drug substance specification:
   a) Please add a test with appropriate acceptance criteria (b) (4);
   b) Please add a test with appropriate acceptance criteria for pH;
   c) In addition to the heavy metal test by USP <231>, add a test with appropriate acceptance criteria for (b) (4) content. Please refer to USP <232>, USP <233>, and ICH Q3D for further guidance.

2. In reference to Section 3.2.P.3.3 of the NDA submission concerning the manufacturing process description:
   (b) (4)

3. The information provided in Section 3.2.P.3.4 of the NDA is not adequate. Please refer to ICH M4Q(R1) and submit the necessary information accordingly. In this section, all critical process controls and their associated numeric ranges, limits, or acceptance criteria should be identified and justified and a brief description of the test provided. Any experimental data to support the justification should be included in this section as well. Critical process control values from relevant batches should be provided only as part of the justification.

4. In reference Section 3.2.P.5.1 of the NDA submission concerning the drug product specification:

a) Update the acceptance criteria for Particular Matter test to comply with the current version of USP [redacted]
b) Given that the API is [redacted], we recommend a test with an appropriate acceptance criterion [redacted] be included in the drug product specification. The acceptance criteria should be adequately justified by experimental data;
c) The drug product specification in Table 2.3.P-15 lists [redacted] as one of the identity tests. This is not consistent with the information provided in other section of the NDA submission. Please reconcile.
d) Please tighten the [redacted] limit from NMT [redacted]% to NMT [redacted]% based on available batch analysis data and stability data.

5. Your interpretation of the ICH Q6A, Decision Tree #2 does not seem to be correct. According to Q6A, the "A" value in your equation should be the estimated "maximum increase in the degradation product at shelf life", not the projected value as you stated. As such, some of the proposed acceptance criteria are not fully justified. Based on the available batch data and stability data, we recommend that acceptance criteria be tightened for the following attributes:

[redacted]

6. In reference to Section 3.2.P.5.3 concerning the method validation (PR-10-00185):
   a) Your acceptance criteria of %RSD [redacted]% for precision [redacted] are considered high. We recommend that these acceptance criteria be tightened to NMT [redacted]% for [redacted] precision for impurity tests.
   b) In the validation report (PR-10-00185), you state that the impurity [redacted] degraded from [redacted]% in the test solution. Please discuss the suitability of the analytical method for this particular impurity.
   c) It appears that only precision test has been revalidated after the HPLC method revision. We recommend that [redacted] precision tests be repeated after the revision of the HPLC method.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWE
12/03/2013