

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208744Orig1s000

CLINICAL REVIEW(S)

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	208744
Applicant Name	Accord Healthcare Inc.
Date of Submission	September 1, 2015
PDUFA Goal Date	July 30, 2016
Established (USAN) Name	Tigecycline for Injection
Dosage Forms / Strength	Powder for injection, 50 mg/vial
Proposed Indications	<ol style="list-style-type: none"> 1. Complicated Intra-abdominal Infections 2. Complicated Skin and Skin Structure Infections 3. Community-Acquired Bacterial Pneumonia
Recommended Action:	Complete Response

Material Reviewed/Consulted	Names of Discipline Reviewers
Action Package including:	
Pharmacology Toxicology Review	Wendelyn Schmidt PhD
Product Quality Application Technical Lead	Dorota Matecka PhD
Cross-Discipline Team Leader Review	Dorota Matecka PhD
Medical Officer Review	Dmitri Iarikov MD PhD
Clinical Microbiology Review	Kerian Grande Roche PhD
Clinical Pharmacology Review	Zhixia (Grace) Yan PhD

1.0 Introduction

NDA (b) (4), Tigecycline for Injection, 50 mg/vial submitted by Accord Healthcare Inc., provides for a new formulation of injectable tigecycline to be used for the treatment of the same indications as listed in the labeling for Tygacil (tigecycline), NDA 21821 held by Pfizer. This NDA was submitted under Section 505(b)(2) of the Food Drug and Cosmetic Act. Tygacil is approved for the treatment of adults for the following indications:

1. Complicated Intra-abdominal Infections
2. Complicated Skin and Skin Structure Infections
3. Community-Acquired Bacterial Pneumonia

2.0 Background

The proposed drug product, Tigecycline for Injection, 50 mg/vial is a new formulation of tigecycline for injection. The proposed drug product differs from the listed drug in that it contains maltose instead of lactose (b) (4).

For a detailed discussion of NDA 208744, please refer to discipline specific reviews and the Cross-Discipline Team Leader Review.

3.0 Product Quality

The OPQ review team has identified several deficiencies with the drug substance, drug product, and manufacturing facilities.

The chemistry manufacturing and controls information for the drug substance has been provided via a reference to DMF Type II (b) (4) held by (b) (4) .. DMF (b) (4) is noted to be deficient in review dated December 07, 2015. The deficiencies were conveyed to the DMF holder on December 07, 2015. As the deficiencies have not yet been resolved, DMF (b) (4) is inadequate to support this NDA.

The proposed drug product, Tigecycline for Injection, 50 mg/vial, is an orange lyophilized powder or cake supplied in a clear glass vial and contains the same active ingredient in the same amount as the listed drug Tygacil. However, (b) (4) (lactose) in Tygacil has been replaced with the same amount of (b) (4) (maltose) in the proposed formulation. The Applicant requested a biowaiver for their proposed drug product. The Biopharmaceutics reviewer notes that inclusion of (b) (4) maltose monohydrate instead of lactose monohydrate is not expected to have an impact on the disposition of tigecycline and hence the request for a waiver of the requirement to conduct an in vivo bioavailability/bioequivalence study for their proposed product is granted. Also, information provided for the drug product from the product quality microbiology perspective (i.e., sterility assurance) was found to be acceptable.

The container closure system for the proposed drug product include USP (b) (4) clear tubular glass vial with (b) (4) seal. Information provided for the proposed container closure system was generally found acceptable. Additional information regarding the suitability of the proposed container/closure system, i.e., the results of the extractable/leachable studies using the reconstituted solutions of the proposed drug product was requested. However, this information has not been yet provided.

The proposed drug product specification was found adequate. The proposed expiration dating of 24 months is not supported by the stability data submitted and cannot be granted at this time.

The drug product manufacturing facility, Intas Pharmaceuticals Limited, was found acceptable by the Office of Process and Facilities (OPF). However, based on the most recent inspection of the drug substance facility, [REDACTED] (b) (4), OPF determined that this facility is not acceptable to support the NDA. Therefore, the overall recommendation of “Withhold” was provided by OPF for this NDA.

The overall recommendation from the Product Quality perspective is Complete Response. I agree with their assessment.

4.0 Microbiology

Kerian Grande Roche, PhD, is the clinical microbiology reviewer for this application. No new clinical microbiology information was submitted in this application. Dr. Grande Roche recommends approval from a clinical microbiology perspective. Labeling revisions proposed by Dr. Grande Roche will be incorporated in final labeling.

5.0 Pharmacology-Toxicology

Wendelyn Schmidt, PhD, is the pharmacology-toxicology reviewer for this application. Labeling recommendations provided by Dr. Schmidt will be incorporated in final labeling.

6.0 Clinical Pharmacology

Zhixia (Grace) Yan, PhD, is the clinical pharmacology reviewer for this application. No new clinical pharmacology information was submitted in this application. Labeling recommendations will be addressed during the next review cycle.

7.0 Clinical Efficacy/Safety

Dmitri Iarikov, MD, PhD, is the clinical reviewer for this application. No new clinical studies were submitted in this NDA. From a safety standpoint, maltose in the proposed product can interfere with the readings of some blood glucose monitors resulting in falsely elevated glucose levels. This could lead to either unrecognized and, consequently, untreated hypoglycemia or inappropriate insulin administration which could also lead to hypoglycemia. Dr. Iarikov recommends that information about unrecognized hypoglycemia should be added to the Boxed Warning. This issue will be further discussed during the next review cycle as labeling was not addressed during this review. Dr. Iarikov recommends a complete response due to outstanding product quality issues. I agree with his assessment.

8.0 Labeling

As a complete response letter will be issued, labeling was not addressed in this review cycle and will be reviewed once a complete response to the deficiencies is submitted.

9.0 Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. As none of these criteria are applicable, this NDA is exempt from PREA requirements.

10.0 Other Regulatory Issues

The listed drug, Tygacil (tigecycline, NDA 21821) has the following unexpired patents listed in the Orange Book¹:

- 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. 9,254,328 - Expiry Date: March 13, 2026

Accord Pharmaceuticals Inc. submitted Paragraph III Certification for patent number RE40183 (expiration date April 09, 2016) and Paragraph IV Certification for patents 7,879,828; 8,372,995; and 8,975,242.

On September 11, 2015, the Applicant certified that notice had been provided to the owner of the patents which are the subject of the Paragraph IV certifications or its representatives, and also to the holder of the approved application for the listed drug (Tygacil).

On December 17, 2015, the Applicant provided documentation of receipt of notice as it pertains to the Paragraph IV patent certification contained in NDA (b) (4) also provided notice of the commencement of litigation within the statutory 45-day period.

On April 1, 2016, the Applicant submitted a Paragraph IV Certification for an additional patent No. 9,254,328, which was not listed in the Orange Book at the time of NDA submission. The Applicant has certified that at the time of the filing of this amendment, it has given notice to the owner, or its representatives, of the patents which are the subject of the certification, and also to the holder of the approved application for the reference listed drug.

On July 08, 2016, the Applicant informed the Agency that Accord Healthcare Inc. and Intas Pharmaceuticals Ltd. have been sued by Pfizer Inc., Wyeth LLC, Pfizer Pharmaceuticals LLC,

1

http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021821&Product_No=001&table1=OB_Rx; accessed July 22, 2016

PF Prism C.V. and Pfizer Manufacturing Holdings LLC for U.S patent Nos. 7879828, 8372995, and 8975242.

11.0 Recommended Regulatory Action

I agree with the recommendations made by the review team and the CDTL that the NDA not be approved at this time. A complete response will be issued identifying the following deficiencies:

1. Your application references Drug Master File (DMF) (b) (4). This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on December 7, 2015. These deficiencies must be adequately addressed before this application can be approved. In your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.
2. The proposed expiration dating of 24 months for the drug product, Tigecycline for Injection, is not supported by the currently available stability information. Provide updated stability data for the three drug product registration batches to support the proposed drug product expiration dating.
3. Provide results of the extractable and leachable studies for the proposed (b) (4) using suitable solvents and the reconstituted solutions of the proposed drug product, Tigecycline for Injection, with the proposed reconstitution agents.
4. During a recent inspection of the (b) (4) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of these deficiencies is required before this NDA may be approved.

In addition, the patent owner and/ or approved application holder has initiated a patent infringement suit against the Applicant with respect to patents 7879828, 8372995 and 8975242 in the United States District Court for the District of Delaware (Pfizer Inc, Wyeth LLC, Pfizer Pharmaceuticals LLC, PF Prism C.V. and Pfizer Manufacturing Holdings LLC Plaintiffs, v. Accord Healthcare, Inc., Accord Healthcare Ltd., and Intas Pharmaceuticals Ltd., Defendants).

Therefore, final approval cannot be granted until, expiration of the 30-month period beginning on the date of receipt of the 45-day notice, unless the court has extended or reduced the period or the date the court decides that the patents are invalid or not infringed, or the listed patents have expired.

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

/s/

SUMATHI NAMBIAR
07/22/2016

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dorota Matecka, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	208744
Applicant	Accord Healthcare Inc.
Date of Submission	September 1, 2015
PDUFA Goal Date	July 30, 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:	<i>Complete Response</i>

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

1. Introduction

This 505(b)(2) NDA submitted by Accord Healthcare Inc. (Accord) 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 Accord, 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 (b) (4) (i.e., maltose 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 the listed drugs, a biowaiver for conducting in-vivo bioequivalence studies was requested by the Applicant.

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 is one other tigecycline generic IV formulation approved for use in humans in the US at this time. As discussed above, the drug product proposed by Accord 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. Product Quality

The Product Quality Team from the Office of Pharmaceutical Quality (OPQ) included the following individuals:

Quality Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION/BRANCH
Drug Substance	Haripada Sarker	ONDP/DNAP I/Branch I
Drug Product	Yong Wong	ONDP/DNDP I/Branch III
Process	David Anderson	OPF/DPA III/Branch VII
Microbiology	Yuansha Chen	OPF/DMA/Branch II
Facility	Denise DiGaudio	OPF/DIA/Branch II
Biopharmaceutics	Om Anand	ONDP/DBP/Branch I
Regulatory Business Process Manager	Navi Bhandari	OPRO
Environmental Assessment (EA)	Yong Wong	ONDP/DNDP I/Branch III
Application Technical Lead	Dorota Matecka	ONDP/DNDP I/Branch III

The OPQ review team has identified several deficiencies across the following product quality areas: drug substance, drug product, and manufacturing facilities.

The chemistry manufacturing and controls information for tigecycline drug substance has been provided via a reference to DMF Type II (b)(4) held by (b)(4). DMF (b)(4) has been found to be deficient via a chemistry review dated December 7th, 2015 referenced for another application. The deficiencies were conveyed to the DMF holder on December 7, 2015; however, they have not been addressed as of the date of OPQ review. Therefore, Dr. Sarker concluded that DMF (b)(4) remains inadequate to support this NDA.

The proposed drug, Tigecycline for Injection, 50 mg/vial, is an orange lyophilized powder or cake supplied in a clear glass vial and contains the same active ingredient in the same amount as the listed drug Tygacil®. However, (b)(4) (lactose) in Tygacil® has been replaced with the same amount of (b)(4) (maltose) in the currently proposed formulation. Therefore, the Applicant requested a biowaiver for their

proposed drug product. Dr. Anand concluded based on his review that inclusion of (b) (4) maltose monohydrate instead of lactose monohydrate is not expected to have an impact on the disposition of tigecycline from the proposed formulation as compared to the listed drug. Therefore, the Applicant's request for a waiver of the requirement to conduct an in vivo bioavailability/bioequivalence study for their proposed product is granted.

The manufacturing process for the proposed drug product includes: (b) (4) Several information requests were sent to the Applicant in the course of the NDA review and additional information regarding the drug product manufacturing process particularly the (b) (4) step was provided. Dr. Anderson has found this information acceptable. In addition, information provided for the drug product from the product quality microbiology perspective (i.e., sterility assurance) was found acceptable by Dr. Chen.

The container closure system for the proposed drug product include USP (b) (4) clear tubular glass vial with (b) (4) seal. Information provided for the proposed container closure system was generally found acceptable. Additional information regarding the suitability of the proposed container/closure system, i.e., the results of the extractable/leachable studies using the reconstituted solutions of the proposed drug product was requested by the Agency; however, this information has not been yet provided. The proposed drug product specification was found adequate; however, the proposed expiration dating of 24 months is not supported by the stability data submitted in the NDA and cannot be granted at this time. Therefore, Dr. Wong concluded that information provided for the proposed drug product is inadequate.

The drug product manufacturing facility, Intas Pharmaceuticals Limited, was found acceptable by the Office of Process and Facilities (OPF). However, based on the most recent inspection of the proposed drug substance facility, (b) (4) the OPF determined that this facility is not acceptable to support the current NDA. Therefore, the overall recommendation of "Withhold" was provided by OPF for this NDA.

Based on the above findings, the current overall recommendation from the Product Quality perspective is Complete Response (refer to the OPQ reviews entered into Panorama on July 1, 2016).

4. Nonclinical Pharmacology/Toxicology

Dr. Wendy Schmidt was the Pharmacology/Toxicology Reviewer for this application. Dr. Schmidt stated that there are no pharmacology/toxicology objections to approval of this NDA; however, several labeling revisions will need to be included in the package insert (for details refer to the review dated July 1, 2016 in DARRTS).

5. Clinical Pharmacology

The Clinical Pharmacology Reviewer, Dr. Zhixia (Grace) Yan, stated that this application does not contain any new clinical pharmacology information; thus, this application is acceptable from a clinical pharmacology perspective. However, the Clinical Pharmacology Review Team has identified a potential risk of unrecognized hypoglycemia associated with the proposed drug product containing maltose due to interference with blood glucose testing. A comment regarding this issue was conveyed to the Applicant and a relevant revision was proposed to be included in Section 7.3 of the Package Insert "Blood Glucose Testing". However, the final decision regarding this issue was deferred to the Clinical Reviewer of this application. In addition, several other labeling revisions to Section 12.3 were recommended by Dr. Yan (review dated June 21, 2016 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 June 23, 2016 in DARRTS).

7. Clinical/Statistical – Efficacy

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

Dr. Iarikov stated that this 505(b)(2) NDA, which provides for a new IV formulation of tigecycline (and the same active pharmaceutical ingredient, same strength, dose and concentration are proposed), does not contain any clinical studies as 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). Therefore, supportive information is derived from the tigecycline labeling and published literature. Dr. Iarikov commented also on the use of maltose as a new excipient in the proposed formulation stating that maltose can interfere with the readings of some blood glucose monitors resulting in falsely elevated glucose levels, which may lead to unrecognized hypoglycemia or to inappropriate insulin administration.

In his recommendation, Dr. Iarikov stated 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. Therefore, as the current 505(b)(2) NDA application for tigecycline relies on FDA's previous findings of safety and effectiveness for the listed drug (Tygacil®), Dr. Iarikov recommends this application for approval noting however, that the product quality deficiencies will preclude the approval action for this NDA

at this time. Dr. Iarikov further noted that if the proposed formulation of tigecycline is eventually approved, the risk of unrecognized hypoglycemia will need to be clearly emphasized in the labeling (review dated June 24, 2016 in DARRTS).

Dr. Rubin stated that this submission did not require statistical review since there were no clinical studies provided in the submission (review dated November 5, 2015 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). Dr. Iarikov noted in his review that 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.” In addition to adverse reactions associated with tigecycline, the proposed product has a unique safety concern related to its inactive ingredient, maltose. As mentioned above, maltose can interfere with the readings of some blood glucose monitors resulting in falsely elevated glucose levels, which may lead to unrecognized hypoglycemia or to inappropriate insulin administration. Dr. Iarikov stated that the strategy to mitigate the risk of unrecognized hypoglycemia associated with the proposed product will need to be addressed in detail when this NDA is resubmitted. For details regarding safety assessment of tigecycline, refer to the review by Dr. Dmitri Iarikov (dated June 24, 2016 in DARRTS).

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

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. 9,254,328 - Expiry Date: March 13, 2026
- US Patent No. RE40,183 - Expiry Date: April 9, 2016

In the initial NDA submission, Accord submitted Paragraph III Certification for patent number RE40183, which is now expired. In addition, Accord has submitted Paragraph IV Certification [per 21 CFR 314.50(i)(1)(4)] regarding patents 7,879,828; 8,372,995; and 8,975,242 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) NDA is submitted.

Subsequently, the Applicant submitted an NDA amendment dated January 21, 2016 to certify that notices regarding the "Paragraph IV" certification were delivered to the owner of the patents which are the subject of the Paragraph IV certifications or its representatives, and also to the holder of the approved application for the Listed Drug (TYGACIL®, NDA 21821). The NDA was further amended on March 28, 2016 with a Paragraph IV Certification for additional Patent No. 9,254,328, which had not been listed in the Orange Book at the time of NDA submission.

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 by DMEPA (review by Deborah Myers, RPh, MBA, dated June 22, 2016, in DARRTS). However, the labeling will not be finalized during the current review cycle, due to the issuance of a Complete Response.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with the assessments made by the review team and recommend the issuance of a Complete Response for this NDA.

- Risk Benefit Assessment

The risk-benefit assessment for this application focused on the significant product quality issues identified during the review cycle by the OPQ review team which includes the following product quality areas: drug substance, drug product, and manufacturing facilities.

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number	208744
Priority or Standard	Standard
Submit Date	9/30/2015
Received Date	9/30/2015
PDUFA Goal Date	7/30/2016
Division / Office	Division of Anti-Infective Products
Reviewer Name	Dmitri Iarikov, MD, PhD
Review Completion Date	June 21, 2016
Established Name	Tigecycline for injection
Trade Name	Not applicable
Therapeutic Class	Tetracycline class antibacterial
Applicant	Accord Healthcare Inc.
Formulation	Intravenous injection, 50 mg/vial
Dosing Regimen	Initial dose of 100 mg, followed by 50 mg every 12 hours
Indications	Severe hepatic impairment (Child Pugh C): Initial dose of 100 mg followed by 25 mg every 12 hours. Complicated skin and skin structure infections Complicated intra-abdominal infections Community-acquired bacterial pneumonia
Intended Population	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical reviewer perspective this 505 (b)(2) application for tigecycline for the indications of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia may be approved.

However, there are several chemistry, manufacturing, and controls (CMC) deficiencies requiring resolution before the product can be approved. The main issues are the inadequacy of the Drug Master File (DMF) to which the drug substance is cross-referred to and the (b) (4) hold imposed on the drug substance manufacturer. These issues will not be resolved during this review cycle due to insufficient time left and the application will not be approved.

1.2 Risk Benefit Assessment

This 505(b)(2) NDA application for tigecycline relies on FDA's previous findings of safety and effectiveness for the listed drug, Tygacil. No new clinical information was submitted in this NDA. Tigecycline remains 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.

Notably, in addition to adverse events associated with tigecycline as an active ingredient, the proposed product has a unique safety concern related to its inactive ingredient, maltose. In the proposed product as compared to the listed drug Tygacil maltose substitutes for lactose (b) (4). Maltose can interfere with the readings of some blood glucose monitors resulting in falsely elevated glucose levels which may lead to unrecognized hypoglycemia or to inappropriate insulin administration.

If the proposed formulation of tigecycline is eventually approved, the risk of unrecognized hypoglycemia will need to be clearly emphasized in the labeling. In addition, other measures mitigating this risk may need to be discussed. The reader is referred to section 7 of this review for more detail.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable since the application will not be approved during this review cycle.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable since the application will not be approved during this review cycle.

2 Introduction and Regulatory Background

2.1 Product Information

Tigecycline is a tetracycline-class antibacterial drug. Tigecycline inhibits protein translation in bacteria by binding to the 30S ribosomal subunit, blocking entry of aminoacyl tRNA into the A site of the ribosome and preventing incorporation of amino acid residues into elongating peptide chains. Tigecycline is considered bacteriostatic; however, tigecycline demonstrated bactericidal activity against *S. pneumoniae* and *L. pneumophila*.

Molecular structure of Tigecycline is presented in Figure 1.

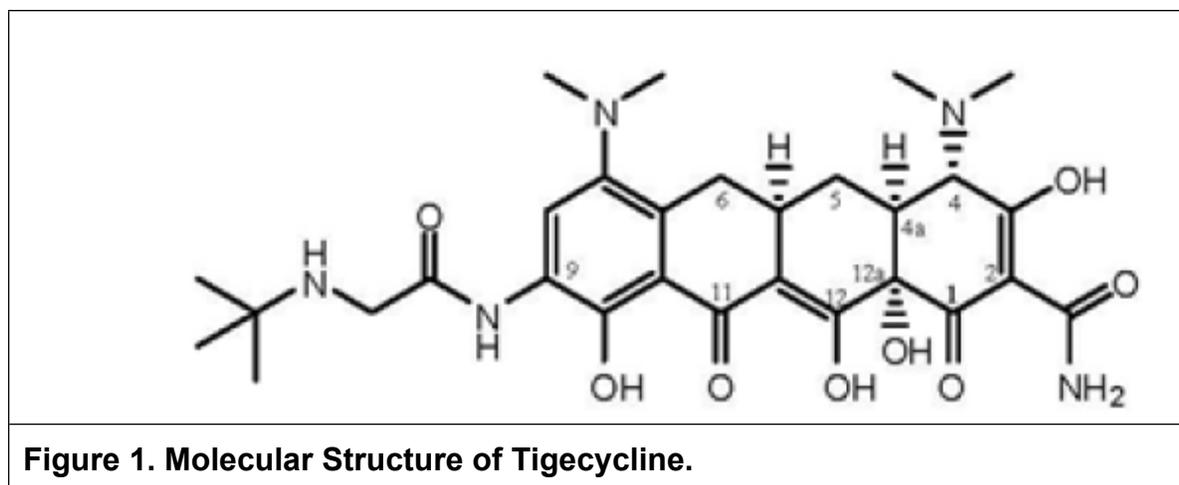


Figure 1. Molecular Structure of Tigecycline.

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.

The product of this 505 (b)(2) NDA differs from the listed drug with respect to ^{(b) (4)} [REDACTED]. The applicant's product contains maltose monohydrate whereas the listed drug contains lactose monohydrate. Otherwise the applicant's product has the same active and inactive ingredients, strength, route of administration, and conditions of use as the listed drug, Tygacil (tigecycline) for injection. Each tigecycline vial contains 50 mg tigecycline lyophilized powder for reconstitution and intravenous infusion.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 lists selected antibacterial drugs that are approved for the proposed indications and could be used in similar patient populations.

Table 1: Selected Antibacterial Drugs Approved for Proposed Indications

Antibacterial drugs	Indications		
	Complicated skin and skin structure infections	Community acquired pneumonia	Complicated intra-abdominal infections
Cefazolin	X	X ^a	-
Cefepime	-	X	X
Ceftaroline	X	X	-
Ceftazidime	X	X ^b	X
Ceftazidime and Avibactam	-	-	X
Ceftriaxone	X	X	X
Ceftolozane and Tazobactam	-	-	X
Ciprofloxacin	X	X ^b	X
Dalbavancin	X	-	-
Daptomycin	X	-	-
Ertapenem	X	X	X
Imipenem and cilastatin	X	X	X
Levofloxacin	X	X	-
Linezolid	X	X	-
Meropenem	X	-	X
Moxifloxacin	X	X	X
Oritavancin	X	-	-
Piperacillin-tazobactam	X	X	X
Tedizolid	X	-	-
Telavancin	X	-	-
Vancomycin	X	X ^b	-

^a Cefazolin is approved for respiratory tract infections
^b Approved for lower respiratory tract infections

2.3 Availability of Proposed Active Ingredient in the United States

Tigecycline is marketed in the United States as Tygacil under NDA 21821 sponsored by PF Prism C.V.

2.4 Important Safety Issues With Consideration to Related Drugs

In comparative clinical trials tigecycline was found to be associated with an increase in all-cause mortality as compared to comparators. In September 2013 the tigecycline label was revised to include a boxed warning containing the following information:

All-cause mortality was higher in patients treated with TYGACIL than comparators in a meta-analysis of clinical trials. The cause of this mortality risk difference of 0.6% (95% CI 0.1, 1.2) has not been established. TYGACIL should be reserved for use in situations when alternative treatments are not suitable.

Several investigations of tigecycline-associated mortality have been conducted by FDA. In randomized clinical trials of tigecycline, more deaths were noted in the tigecycline arm in the initial complicated skin and skin structure infections (cSSSI) and complicated intra-abdominal infections (cIAI) tigecycline trials as well as in the majority of subsequent trials of cIAI, hospital-acquired pneumonia (HAP), community-acquired bacterial pneumonia (CABP), resistant pathogens (RP), and diabetic foot infection (DFI).

In a meta-analysis of thirteen comparative trials, an increase in the risk of all-cause mortality of approximately 1% among tigecycline-treated patients was noted. Although for each indication, the mortality difference was not statistically significant, mortality in tigecycline-treated patients was numerically greater in every infection, and was particularly greater in ventilator-associated pneumonia (VAP), a subgroup of HAP. Tigecycline is not approved for HAP because of an unacceptably low cure rate and excess mortality relative to active-control.

An analysis of mortality in all trials conducted for approved indications -cSSSI, cIAI, and CABP, including three post-market trials showed an adjusted mortality rate of 2.5% for tigecycline and 1.8% for comparator, respectively. The adjusted risk difference for mortality stratified by trial weight was 0.6% (95% CI 0.0, 1.2).

Overall, in comparative clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with tigecycline (7%) versus comparators (6%). Serious adverse events of sepsis/septic shock were more frequently reported for subjects treated with tigecycline (2%) versus comparators (1%).

The most common treatment-emergent adverse reactions were nausea and vomiting which generally occurred during the first 1 – 2 days of therapy. The incidence of nausea was 26% in the tigecycline group and 13% in the comparator group. The incidence of vomiting was 18% in the tigecycline group and 9% in the comparator group.

The reader is referred to the tigecycline labeling for additional information [1]. For safety concerns associated with the proposed formulation of tigecycline the reader is referred to section 7 of this review.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A Pre-Investigational New Drug Application (PIND) file for tigecycline for injection was filed on June 27, 2013 and acknowledged on July 09, 2013. Subsequently FDA opened PIND 119059. On August 16, 2013 FDA provided comments to the sponsor questions on the development plans for tigecycline for injection.

NDA 208744 for tigecycline Injection 50 mg/mL was submitted pursuant to section 505(b)(2) on September 30, 2015 and received on September 30, 2015. There had been no other significant presubmission regulatory activity related to this NDA.

3 Ethics and Good Clinical Practices

Not applicable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The reader is referred to the tigecycline labeling for additional information on clinical pharmacology, clinical microbiology, pharmacodynamics and pharmacokinetics of tigecycline [1].

4.1 Chemistry Manufacturing and Controls

There are several deficiencies related to chemistry, manufacturing, and controls requiring resolution before the product can be approved but that remain unresolved at the time this review is written. The main issues are the deficiency in the Drug Master File (DMF) to which the drug substance is cross-referred to and the (b) (4) hold imposed on the drug substance manufacturer.

Tigecycline is a tertiary-butyl glycyI substituted analogue of minocycline. The applicant cross-referred all drug substance information to drug master files (b) (4). The drug substance information in the cross-referred DMFs was found to be inadequate. The applicant was asked to communicate with the DMF holder to resolve the deficiencies. The response is pending at the time this review is written.

The other major CMC deficiency is the (b) (4) hold imposed on the drug substance manufacturer. The resolution of this deficiency will require the inspection of the manufacturing facility that will not be completed during the review cycle of this NDA due to insufficient time left.

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The reader is referred to the integrated product quality review by Hari Sarker (drug substance), Yong Wong (drug product), David Anderson (process), Yuansha Chen (microbiology), Denise Digiulio (facility), and Om Anand (biopharmaceutics) for more detail.

4.2 Clinical Microbiology

The reader is referred to the clinical microbiology review.

4.3 Nonclinical Pharmacology/Toxicology

The reader is referred to the pharmacology/toxicology review.

5 Sources of Clinical Data

No clinical studies have been conducted by the applicant and only data from published sources have been provided.

6 Review of Efficacy

Efficacy Summary

No new information changing prior assessments of the risk-benefit profile of tigecycline have been identified.

7 Review of Safety

Safety Summary

In addition to adverse reactions associated with tigecycline as described in section 2.4 of this review, the proposed product has a unique safety concern related to its inactive ingredient, maltose. In the proposed product as compared to the listed drug Tygacil maltose substitutes for lactose (b) (4). Maltose can interfere with the readings of some blood glucose monitors resulting in falsely elevated glucose levels. This could lead to either unrecognized and, consequently, untreated hypoglycemia or inappropriate insulin administration which could also lead to hypoglycemia.

The interference may occur when glucose test strips with glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase are used. These test strips cannot distinguish between glucose and non-glucose sugars (i.e., maltose, galactose, and xylose) [2, 3]. Notably, two major glucose detecting systems dominate the market: glucose oxidase-based systems and glucose dehydrogenase-based systems using pyrroloquinoline quinone (GDH-PQQ) as a cofactor [3]. The older

glucose oxidase-based glucometers, while being able to distinguish between glucose and non-glucose sugars have been replaced by GDH-PQQ based glucometers because of lower sensitivity of GDH-PQQ based glucometers to oxygen.

Inaccurate blood glucose testing due to interference of maltose with glucose monitors is a recognized drug-device interaction for several FDA approved products including ANTHRASIL, an anthrax immune globulin [4], EXTRANEAL (icodextrin), a peritoneal dialysis solution [5], and ORENCIA (abatacept), a selective T cell costimulation modulator [6]. The package inserts of the two of these products, i.e., ANTHRASIL and EXTRANEAL include boxed warnings informing on the risk of unrecognized hypoglycemia related to interference with blood glucose testing. The package insert of ORENCIA does not include warnings but includes a subsection on blood glucose testing in the drug interactions section of the package insert. Methods that do not react with maltose are recommended to avoid falsely elevated blood glucose levels when these products are used.

The amount of maltose included in the proposed formulation of tigecycline is 100 mg of maltose per a 50 mg/vial of tigecycline. The maximum 24-hour amount of maltose that could be administered is 400 mg considering that tigecycline initial dose is 100 mg (2 vials) followed by 50 mg (1 vial) every 12 hours. The degree of interference with blood glucose readings that may be associated with this or any other amount of maltose is not certain. Hence, the comparison of the amount of maltose included in the proposed tigecycline formulation and that included in other maltose-containing products may not be informative. Nevertheless, for EXTRANEAL (icodextrin), the discrepancies between levels measured by improper glucometers and actual values could be significant when levels measure by glucometers were in the 125-133 mg/dL range whereas actual values were in the 29-35 mg/dL ranges [2].

Importantly, tigecycline is administered daily up to 14 days in patients with severe infections where fluctuations in blood glucose levels is common and accuracy of blood glucose measurements is critical. Unrecognized hypoglycemia due to falsely normal glucose readings or due to inappropriate insulin administration in response to falsely elevated glucose levels represents a serious safety concern.

From this reviewer perspective the risk of unrecognized hypoglycemia should be added to the boxed warning. In addition the information that the product contains maltose and carries the risk of interfering with blood glucose readings should be made more prominent on the container label.

Moreover, there is concern that this risk may not be fully mitigated by a boxed warning. The listed drug and a generic tigecycline product available on the market do not contain maltose. Consequently, health care providers will not expect falsely elevated glucose readings in association with tigecycline. Furthermore, a prescriber may consult the package insert of the listed drug, where the risk of unrecognized hypoglycemia is not

described rather than look at the package insert for the proposed product since major differences between the formulations of the same drug are not expected.

The strategy to mitigate the risk of unrecognized hypoglycemia associated with the proposed product warrants further discussion. At this time the magnitude of the risk is not clear. No data on the expected degree of errors in glucose readings that may be caused by the presence of the proposed amount of maltose were provided. The Applicant was informed about concerns related to the risk of unrecognized hypoglycemia. Since the application will not be approved during this review cycle, the issue of unrecognized hypoglycemia will be addressed if the application is resubmitted.

8 Postmarket Experience

No updates to known information on postmarketing experience with tigecycline have been provided in this submission.

9 Appendices

9.2 Labeling Recommendations

The application will not be approved in its present form due to CMC-deficiencies and a Complete Response letter will be issued. Consequently the labeling for this tigecycline product will not be finalized in the current review cycle.

9.3 Advisory Committee Meeting

Not applicable.

10 References

1. *TYGACIL (tigecycline) [package insert]. PF Prism CV, January 2016. Access date: May 28, 2016.*
http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021821s043lbl.pdf.
2. Firanek, C.A., D.T. Jacob, and J.A. Sloand, *Avoidable iatrogenic hypoglycemia in patients on peritoneal dialysis: the risks of nonspecific glucose monitoring devices and drug-device interaction.* J Patient Saf, 2014. **10**(4): p. 218-21.
3. Flore, K.M. and J.R. Delanghe, *Analytical interferences in point-of-care testing glucometers by icodextrin and its metabolites: an overview.* Perit Dial Int, 2009. **29**(4): p. 377-83.
4. *ANTHRASIL [Anthrax Immune Globulin Intravenous (Human)] [package insert]. Cangene corporation, March 2015. Access date: May 31, 2016.*
<http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM439812.pdf>.

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5. *EXTRANEAL (icodextrin) peritoneal dialysis solution [package insert]. Baxter Hlthcare, October 2015. Access date: May 31, 2016.*
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021321s032lbl.pdf.
6. *ORENCIA (abatacept) [package insert]. Bristol Myers Squibb, December 2014. Access date: May 28, 2016.*
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/s/

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06/24/2016