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RESEARCH**

APPLICATION NUMBER:

208744Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality (OPQ) Review

NDA 208744

OPQ Review # 2

Review Date: January 10, 2018
Submission: NDA 208744 Resubmission (Class 2); SDN#18
Submission date: July 18, 2017
OND Division: Division of Anti-Infective Products (DAIP)
Product Name: Tigecycline for Injection, 50 mg/vial
Applicant: Accord Healthcare Inc.

Executive Summary:

NDA 208744 originally submitted on September 30, 2015 was recommended for Complete Response (CR) by the OPQ Review Team due to several product quality deficiencies, which included: 1) inadequate status of the DMF (b) (4) referenced in the NDA for the tigecycline drug substance; 2) lack of adequate stability data to support the proposed drug product expiration dating; and 3) inadequate extractable and leachable information to support the suitability of the proposed drug product container closure system. In addition, the drug substance manufacturing facility was found unacceptable to support the NDA (refer to the OPQ Review # 1 dated July 1, 2016, in Panorama and a CR letter dated July 22, 2016 in DARRTS). The current NDA resubmission (Class 2) includes only responses to the CR comments with no additional updates to other CMC sections. The responses to the CR comments were reviewed and found acceptable. Specifically, the results of the extractables and leachables studies and stability information that includes 24-month stability results for the three representative batches of the drug product were found acceptable (refer to the Drug Product Review and Addendum, Attachment I). Also, the DMF Type II referenced for the tigecycline drug substance (DMF (b) (4)) was recently reviewed for another application and is now considered adequate (refer to the Drug Substance Review, Attachment II). The status of manufacturing facilities was assessed by Dr. Jonathan Swoboda who found them acceptable based on the review of the application and inspectional documents of the facilities responsible for manufacturing the drug product and the drug substance (refer to the Facilities Review, Attachment III). In addition, the Comparability Protocol included in the NDA (b) (4) was revised (b) (4) and resubmitted in the NDA amendment dated December 19, 2017, has been found acceptable (refer to Drug Substance Review Addendum and Facilities Review, Attachments II and III, respectively). Based on the above assessments and the overall recommendation of "Approve" entered by the Office of Process and Facilities (OPF) into Panorama on December 10, 2017, this NDA can be now recommended for approval.

Recommendation:

This NDA is recommended for Approval from the Product Quality perspective.

Attachments

Attachment I (Drug Product - Dr. Yong Wang)

Attachment II (Drug Substance – Dr. Haripada Sarker)

Attachment III (Facilities - Dr. Jonathan Swoboda)

Attachment IV (Risk Table)

Application Technical Lead (ATL) Signature:

Dorota M.
Matecka -S

Digitally signed by Dorota M. Matecka-S
DN: cn=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, ou=CD, ou=CD, ou=CD, ou=CD, ou=CD,
ou=Dorota M. Matecka-S
Date: 2016.01.11 11:21:21 -0500

This NDA is recommended for approval from the Product Quality perspective.

On behalf of the OPQ Review Team

Dorota Matecka, Ph.D., ATL for NDA 208744

Attachment I

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Memorandum

Date	January 9, 2018
NDA	208744
Drug Name/Dosage Form	Tigecycline for Injection, USP/Injection (lyophilized)
Strength	50 mg/Vial
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Applicant	Accord Healthcare Inc.
US agent, if applicable	NA

This memorandum is to address the expiry date of Tigecycline for Injection, reviewed under this NDA. Upon further internal discussion of the stability data, it is concluded that a 24-month expiration dating can be granted based on the 24-month stability data submitted. In addition, a labeling recommendation for revision (b) (4) to a "single-dose" vial was communicated to and accepted by the applicant.



Yong
Wang

Digitally signed by Yong Wang

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Balajee
Shanmugam

Digitally signed by Balajee Shanmugam

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Attachment IV

Risk Assessment

From Initial Risk Identification			Review Assessment		
From Initial Risk Identification	Review Assessment	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
		H, M, or L		Acceptable or Not Acceptable	
Assay /Stability	Formulation Raw materials Process parameters Scale/equipment Site	L		Acceptable (24-month expiry dating was granted for the DP based on the 24 months of stability data provided in the NDA for three registration batches)	(b) (4)
Uniformity of Dose	Process parameters	L	Adequate in-process controls	Acceptable	
Reconstitution time	Formulation Process parameters Raw materials	M	(b) (4)	Acceptable	
Leachables (b) (4)	Formulation Container closure	L	Powder for injection; E/L study results provided	Acceptable	
Sterility	Process parameters	H		Acceptable	
Particulate matter	Formulation Process parameters	M	Release and stability testing per USP <788>	Acceptable	
Facilities*	Sites	H*		Acceptable*	

* Life-cycle Consideration outlined in (b) (4): CDER/OPF recommends the corrective actions outlined by the firm be reviewed and verified during the next scheduled surveillance inspection, including continued verification of the firm's data integrity program, cleaning validation reports for the FP equipment, documentation practices and controls, and physical storage/warehouse environments (refer to Facilities Review for further details).

**QUALITY ASSESSMENT****Recommendation: Complete Response****NDA 208744
Review # 1**

Drug Name/Dosage Form	Tigecycline for Injection/ Lyophilized Powder for Injection
Strength	50 mg/vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Accord Healthcare Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	9/30/2015	All
Amendment	12/28/2015	Drug Product, Facilities, Biopharmaceutics
Amendment	3/22/2016	Drug Product, Process, Microbiology
Amendment	4/29/2016	Drug Substance, Drug Product, Process
Amendment	6/3/2016	Process, Facilities

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 DiGiulio	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
Laboratory (OTR)	N/A	N/A

OPQ-XOPQ-TEM-0001v02 Effective Date: 13 Mar 2015

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	Deficient	12/7/15	(b) (4)
	III			NA		
	III			NA		
	V			NA		

¹ Adequate, Adequate with Information Request, Deficient, or N/A (there is enough data in the application, therefore, the DMF did not need to be reviewed)

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
pre-IND	119059	pre-IND/pre-NDA meeting

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Adequate	June 8, 2016	Dr. Wendy Schmidt
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has not provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product, tigecycline for injection. The drug substance facility, (b) (4), was found unacceptable by the Office of Process and Facilities, and the overall recommendation of "Withhold" was entered into Panorama for this NDA on June 17, 2016. DMF (b) (4) referenced in the NDA for tigecycline drug substance was found to be inadequate. A deficiency letter was sent to the DMF holder on December 7, 2015; however, a response to these deficiencies has not been yet submitted and the DMF remains inadequate. The expiration dating of 24 months currently proposed for the drug product is not supported by the stability data submitted in the application. Also, the results of the extractable and leachable studies for the proposed (b) (4) were not provided. In addition, the Comparability Protocol that provides (b) (4) could not be assessed since the information currently provided for the drug substance has been found inadequate due to deficiencies identified in DMF (b) (4). The proposed container and carton labels and the package insert are presently under review by the NDA review team.

Therefore, this NDA is currently recommended for Complete Response from the Product Quality perspective.

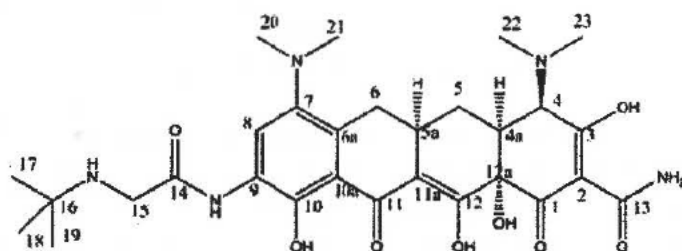
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

A. Drug Substance [Tigecycline] Quality Summary

Chemical Name: (4S,4aS,5aR,12aS)-9-[2-(*tert*-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

Chemical structure:General Properties:

Tigecycline drug substance is an amorphous, hygroscopic, yellow to orange powder freely soluble in DMF, water, ethanol and water (pH below 4.5).

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; however, they have not been addressed as of the date of this review. Therefore, DMF (b) (4) remains inadequate to support this NDA.

B. Drug Product [Tigecycline for Injection] Quality Summary

Tigecycline for Injection, 50 mg/vial, is an orange lyophilized powder or cake supplied in a clear glass vial. The proposed drug product 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. The Applicant requested a waiver for the bioequivalence (BE) requirement for their product, Tigecycline for Injection, 50 mg/vial, which has been granted based on the data provide in the NDA (see section D. Biopharmaceutics Considerations, below).

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.

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.

Information provided for the drug product from the product quality microbiology perspective (i.e., sterility assurance) was found acceptable. The proposed drug product specification was found adequate; however, the proposed expiration dating of 24 months does not appear to be supported by the stability data submitted in the NDA 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 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 for this NDA by OPF.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	N/A
Non Proprietary Name of the Drug Product	Tigecycline for Injection
Non Proprietary Name of the Drug Substance	Tigecycline
Proposed Indication(s) including Intended Patient Population	Complicated skin and skin structure infections, complicated intra-abdominal infections and community-acquired bacterial pneumonia (adults)
Duration of Treatment	Varies with indication (5 to 14 days)
Maximum Daily Dose	150 mg (3 vials)
Alternative Methods of Administration	Intravenous

D. Biopharmaceutics Considerations

Tigecycline for Injection [50 mg/vial], has the same active ingredient, strength, route of administration, and conditions of use as the listed drug, Tygacil® (tigecycline) for Injection, 50 mg/vial. The Applicant's proposed drug product contains the same inactive ingredients in the same concentration as the listed drug (b) (4). The Applicant's drug product formulation contains maltose monohydrate, whereas the listed drug contains lactose monohydrate (b) (4)



QUALITY ASSESSMENT



Inclusion of (b) (4) maltose monohydrate instead of lactose monohydrate is not expected to have an impact on the disposition of tigecycline from the Applicant's proposed formulation as compared to the reference formulation. Therefore, the Applicant's request for a waiver of the requirement to conduct an in vivo bioavailability/bioequivalence study for their proposed product, Tigecycline for Injection [50 mg/vial], is granted.

From the Biopharmaceutics perspective, NDA 208744 for Tigecycline for Injection [50 mg/vial], is recommended for **APPROVAL**.

E. Novel Approaches N/A

F. Any Special Product Quality Labeling Recommendations N/A

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

This NDA is recommended for Complete Response from the Product Quality perspective.

Dorota M.
Matecka-5

Dorota Matecka, Ph.D.

CMC Lead; Branch III; Division of New Drug Products I

July 1, 2016



ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

Tigecycline is a glycylycyclines antibiotic derived from tetracyclines. Tigecycline has a similar mechanism of action as tetracycline antibiotics. It binds to the 30s ribosomal subunit to prevent the aminoacyl tRNA from binding to the A site of the ribosome. It is indicated in patients 18 years of age and older for:

- Complicated skin and skin structure infections
- Complicated intra-abdominal infections
- Community-acquired bacterial pneumonia

Tigecycline is an orange colored powder soluble in water [338.7 mg/ml]. Tigecycline for Injection is a sterile orange colored lyophilized powder or cake. It is an (b) (4) processed sterile product containing no antimicrobial preservatives.

The basis of this 505(b)(2) NDA for Tigecycline for Injection [50 mg/vial] is the approved listed drug Tygacil® (tigecycline) for Injection, which is the subject of an approved NDA 021821.

The listed drug, Tygacil[®] is also an orange lyophilized powder or cake. Each Tygacil[®] single-dose 5 mL or 10 mL vial contains 50 mg tigecycline and 100 mg of lactose monohydrate lyophilized powder for reconstitution for intravenous infusion. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide. The product does not contain preservatives¹.

The mean pharmacokinetic parameters of tigecycline after single and multiple intravenous doses of the listed drug, Tygacil[®], based on pooled data from clinical pharmacology studies are summarized in Table 1².

Table 1. Mean (CV%) pharmacokinetic parameters of Tigecycline

	Single Dose 100 mg (N=224)	Multiple Dose ^a 50 mg every 12h (N=103)
C _{max} (mcg/mL) ^b	1.45 (22%)	0.87 (27%)
C _{min} (mcg/mL) ^c	0.90 (30%)	0.63 (15%)
AUC (mcg·h/mL)	5.19 (36%)	--
AUC _{0-24h} (mcg·h/mL)	--	4.70 (36%)
C _{min} (mcg/mL)	--	0.13 (59%)
t _{1/2} (h)	27.1 (53%)	42.4 (83%)
CL (L/h)	21.8 (40%)	23.8 (33%)
CL _r (mL/min)	38.0 (82%)	51.0 (58%)
V _{ss} (L)	568 (43%)	639 (48%)

^a 100 mg initially, followed by 50 mg every 12 hours

^b 30-minute infusion

^c 60-minute infusion

The comparison of the qualitative and quantitative composition of the proposed drug product and the listed drug [LD] is provided below in Table 2.

Table 2: Comparison of qualitative and quantitative composition of the proposed drug product [Accord's Formulation] and the listed drug [Tygacil[®]] (referred to as RLD in the Table below)

¹ Tygacil label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021821s043lbl.pdf

² Tygacil label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021821s021lbl.pdf

Sr. No.	Ingredients	Accord's Formulation Composition	[RLD] PF PRISM CV's Formulation Composition	RLD Formulation Composition (% w/w)	Accord's Formulation Composition (% w/w)	% Allowed as per IIG
	Strength	50 mg/vial	50 mg/vial	(b) (4)		
1.	Tigecycline	50 mg	50 mg			
2.	Lactose monohydrate	-	100 mg			
3.	Maltose monohydrate	100 mg	-			
4.	Hydrochloric Acid	(b) (4)				
5.	Sodium Hydroxide					

NM: Not Mentioned

The comparative osmolality and pH of the exhibit batches vs. Tygacil® are summarized below:

Table 3: Comparison of pH and osmolality between Accord's proposed product and LD Tygacil® for Injection: Reconstituted product (10 mg/mL of Tigecycline at 20 – 25 °C)³

Drug Product	RLD Product TYGACIL® (tigecycline) for Injection	Applicant's Product Tigecycline for Injection, USP		
Strength	50 mg/vial	50 mg/vial		
Batch number	AJ7H12	R05140	R06215	R06682
Date of Mfg.	---	05/2014	06/2014	06/2014
Exp. Date	04/2016	04/2016	05/2016	05/2016
Test Parameters				
Osmolality				
0.9% Sodium Chloride Injection	385 mOsmol/Kg	398 mOsmol/Kg	405 mOsmol/Kg	404 mOsmol/Kg
5% Dextrose Injection	382 mOsmol/Kg	425 mOsmol/Kg	428 mOsmol/Kg	425 mOsmol/Kg
Lactated Ringer's Injection	349 mOsmol/Kg	382 mOsmol/Kg	385 mOsmol/Kg	383 mOsmol/Kg
pH of Reconstituted solution				
0.9% Sodium Chloride Injection	5.08	4.86	4.99	5.00
5% Dextrose Injection	4.93	4.72	4.82	4.82
Lactated Ringer's Injection	5.03	4.86	4.94	4.94

Table 4: Comparison of pH and osmolality between Accord's proposed product and LD Tygacil® for Injection: Diluted product (1.0 mg/mL of Tigecycline at 20 – 25 °C)

³The Applicant did not clearly state the temperature for this table. However in module 3.2.P.2, the Applicant mentioned that the reconstitution studies were carried out at room temperature (20°C - 25°C).

Drug Product	RLD Product TYGACIL [®] (tigecycline) for Injection	Applicant's Product Tigecycline for Injection, USP		
Strength	50 mg/vial	50 mg/vial		
Batch number	AJ7H12	R05140	R06215	R06682
Date of mfg.	--	05/2014	06/2014	06/2014
Exp. Date	04/2016	04/2016	05/2016	05/2016
Test Parameters				
Osmolality				
0.9% Sodium Chloride Injection	297 mOsmol/Kg	299 mOsmol/Kg	299 mOsmol/Kg	302 mOsmol/Kg
5% Dextrose Injection	317 mOsmol/Kg	309 mOsmol/Kg	309 mOsmol/Kg	309 mOsmol/Kg
Lactated Ringer's Injection	271 mOsmol/Kg	293 mOsmol/Kg	289 mOsmol/Kg	291 mOsmol/Kg
pH of Reconstituted solution				
0.9% Sodium Chloride Injection	5.04	4.95	5.05	5.06
5% Dextrose Injection	4.92	4.62	4.69	4.70
Lactated Ringer's Injection	5.25	5.23	5.26	5.26

Table 5: Comparison of pH and osmolality between Accord's proposed product and LD Tygacil[®] for Injection, 50 mg/vial: Diluted product (1.0 mg/mL of Tigecycline at 2 –8 °C)

Drug Product	RLD Product TYGACIL [®] (tigecycline) for Injection	Applicant's Product Tigecycline for Injection, USP		
Strength	50 mg/vial	50 mg/vial		
Batch number	AJ7H12	R05140	R06215	R06682
Date of mfg.	--	05/2014	06/2014	06/2014
Exp. Date	04/2016	04/2016	05/2016	05/2016
Test Parameters				
Osmolality				
0.9% Sodium Chloride Injection	298 mOsmol/Kg	299 mOsmol/Kg	298 mOsmol/Kg	298 mOsmol/Kg
5% Dextrose Injection	315 mOsmol/Kg	308 mOsmol/Kg	311 mOsmol/Kg	312 mOsmol/Kg
Lactated Ringer's Injection	270 mOsmol/Kg	293 mOsmol/Kg	290 mOsmol/Kg	290 mOsmol/Kg
pH of Reconstituted solution				
0.9% Sodium Chloride Injection	5.05	4.95	5.04	5.05
5% Dextrose Injection	4.90	4.62	4.70	4.70
Lactated Ringer's Injection	5.18	5.23	5.26	5.26

Solubility of tigecycline in various diluents is provided below in table 6.

Table 6: Solubility of tigecycline in various diluents

Diluents	Solubility of Tigecycline
0.9% Sodium Chloride Injection	182.226 mg/mL
5% Dextrose Injection	173.761mg/mL
Lactated Ringer's Injection	202.216mg/mL

In vitro protein binding study: Estimation of total and free tigecycline in human plasma (test and reference formulations).

Objective: The in-vitro protein binding study in human plasma was conducted to estimate the concentrations of total and free tigecycline in the test formulation relative to that of the reference formulations.

Method:

- **Measurement of total drug:** Total drug was measured by extracting the drug from the plasma using protein precipitation and analyzed using LC-MS/MS.
- **Measurement of free drug:** Free drug was measured by extracting the drug from the ultrafiltrate plasma using solid phase extraction method and analyzed using LC-MS/MS.
- **Measurement of protein bound drug:** Estimation of total and free drug the bound drug was estimated by using the following calculation:

$$\% \text{ Bound drug} = \frac{(\text{Amount of Total drug} - \text{Amount of free drug})}{(\text{Amount of Total drug})} \times 100$$

Treatment:

- **Test formulation:** Tigecycline for injection 50mg/vial manufactured by: Intas pharmaceuticals Ltd. India. B.No. R06682.
- **Reference product:** Tigecycline for injection 50mg/vial manufactured by: Pfizer Canada Inc. Canada. B.No. AJ91/12.
- **Reference product:** Tigecycline for injection 50mg/viaTigecycline for injection 50mg/vial Manufactured By: Wyeth Pharmaceutical inc. US. B.No. AJ7H12.

Summary of Bioanalytical Method:

The plasma concentrations of Tigecycline in the test and reference formulation samples were determined by a LC-MS/MS method using Tigecycline-d9 as the internal standard and an eight-point calibration curve. For Total Tigecycline, the analyte and internal standard were extracted from the plasma using a protein precipitation method. The estimation of free Tigecycline was conducted by ultrafiltration, solid phase extraction and followed by LC-MS/MS. As part of the process validation, within and between batch precision, accuracy for free Tigecycline and total Tigecycline, recovery of free and total Tigecycline and Tigecycline-d9 in human plasma were monitored. Free (unbound) (%) and protein bound (%)

Tigecycline were back calculated at three concentration levels [QC1 (15 µg/mL); QC2 (7.8 µg/mL) and QC3 (0.05 µg/mL)].

Summary of Results:

Table 7: Comparison of free tigecycline and protein bound tigecycline from two different batches of reference products and one batch the test product

Formulation Number	Sample ID	Total Tigecycline (Conc. ng/mL)	Free Tigecycline (Conc. ng/mL)	Protein Bound Tigecycline (Conc. ng/mL)	% Free Tigecycline	% Protein Bound Tigecycline
Reference Product - Batch No. AJ91/12	HQC	13136.167	3627.942	9508.225	27.6	72.4
	MQC	7286.500	2054.833	5231.667	28.2	71.8
	LQC	49.500	15.888	33.612	32.1	67.9
Reference Product - Batch No. AJ7H12	HQC	14734.833	3967.225	10767.608	26.9	73.1
	MQC	8536.333	2247.387	6288.947	26.3	73.7
	LQC	55.833	14.122	41.712	25.3	74.7
Test Product - Batch No. R06682	HQC	14006.667	4293.303	9713.364	30.7	69.3
	MQC	7753.333	2218.896	5534.438	28.6	71.4
	LQC	51.167	14.985	36.182	29.3	70.7

Conclusion: The % of free and protein bound Tigecycline in plasma is similar for all three formulations at each concentration level tested, hence it is concluded that there was no significant difference between the three formulations with regards to in vitro protein binding.

The Applicant stated that the proposed product contain the same amount of active ingredient and has the same dosage form, indications, dosage regimen and route of administration as the Listed Drug (LD) product Tygacil® (tigecycline) for Injection, 50 mg/vial. The Applicant also claimed that the proposed formulation of Tigecycline for Injection, 50 mg/vial is identical to that of the Listed Drug (LD) product, Tygacil® (tigecycline) for Injection, 50 mg/vial; NDA# 021821 of PF PRISM CV **except for the inactive ingredient lactose monohydrate** (b) (4) **present in the LD formulation, whereas the Applicant's proposed formulation contains maltose monohydrate** (b) (4).

The Applicant justified the presence of the inactive ingredient maltose monohydrate in the proposed formulation as follows:

- Both lactose monohydrate and maltose monohydrate have similar functional category.
- Both lactose monohydrate and maltose monohydrate are disaccharide carbohydrate and are both used in the parenteral formulations.
- Maltose monohydrate is used in a FDA approved formulation for Orencia® (abatacept) lyophilized powder for intravenous infusion, having the same dosage form and the same route administration.

- The maltose monohydrate quantity used in the proposed formulation is below the quantity used in the FDA approved product Orenzia® (abatacept) lyophilized powder for intravenous infusion.
- The maximum daily intake of maltose monohydrate by using the **Applicant's** formulation is 400 mg [Reference package insert of Tygacil®] as compared to 2.0 g for Orenzia® (abatacept) lyophilized powder for intravenous infusion with the same route of administration.

The Applicant provided the following supporting data for a waiver of the bioavailability/bioequivalence requirements:

- Comparison of pH and Osmolality between the Applicant's proposed product and the LD Tygacil® (tigecycline) for Injection, 50 mg/vial (reconstituted and diluted).
- Solubility of tigecycline in the Applicant's proposed and reference reconstituted and diluted solution.
- Estimation of total and free tigecycline in human plasma (test and reference formulations) was performed. The % of free and protein bound Tigecycline is almost similar in test and reference formulations at each level hence it is concluded that there was no significant difference in in vitro protein binding between the three formulations.

Reviewer's Initial Assessment: NOT Satisfactory:

The proposed formulation is similar to the listed drug formulation except with regard to (b) (4) i.e. the proposed product contains maltose monohydrate whereas the list product formulation contains lactose monohydrate. The osmolality and pH of the reconstituted proposed drug product are comparable with the osmolality and pH of the reconstituted listed drug. The Applicant claimed that there is no impact of maltose on the distribution and elimination of tigecycline as supported by the data in the in vitro protein binding study.

As per the Tygacil label⁴, "*the in vitro plasma protein binding of tigecycline ranges from approximately 71% to 89% at concentrations observed in clinical studies (0.1 to 1.0 mcg/mL). The steady-state volume of distribution of tigecycline averaged 500 to 700 L (7 to 9 L/kg), indicating tigecycline is extensively distributed beyond the plasma volume and into the tissues*". As reported by the Applicant, the in vitro plasma protein binding of Tigecycline is similar [approximately 70%] in the test and the reference formulation at each concentration level tested [QC1 (15 µg/mL); QC2 (7.8 µg/mL) and QC3 (0.05 µg/mL)]. The supporting in vitro plasma protein binding study is acceptable.

The Applicant did not provide any information/data regarding the effects of maltose monohydrate on in vivo physiological disposition (distribution, metabolism and excretion) of tigecycline in human subjects.

The following Biopharmaceutics information request was sent to the Applicant [Dated: December 15, 2015]

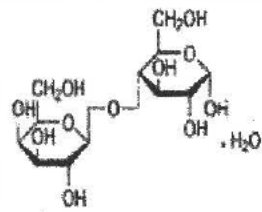
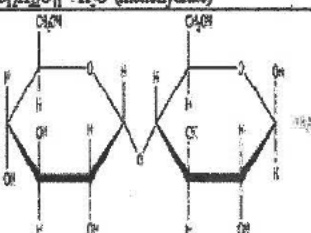
We acknowledge that you have submitted an in vitro plasma protein binding study and you have submitted comparative pH and osmolality data to support your biowaiver request. However, we ask that you submit additional data to address our concern regarding the effects that the inclusion of maltose monohydrate and the lack of lactose monohydrate may have on the disposition of your proposed drug product in relation to the listed drug product in human subjects. Therefore, provide for your proposed product formulated with maltose monohydrate, additional information/data regarding the in vivo physiological disposition (distribution, metabolism and excretion) of tigecycline in human subjects. As supporting evidence, you may also include published literature search results regarding the effects of maltose monohydrate on tigecycline and other drugs.

⁴ Tygacil label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021821s043lbl.pdf

Applicant response [dated: December 28, 2015] to the above stated information request:

The Applicant response is summarized below:

- Maltose monohydrate and lactose monohydrate are commonly used excipients in parenteral formulations (b) (4) and both are disaccharide carbohydrate.

Attribute	Lactose	Maltose
Disaccharide	Glucose + Galactose	Glucose + Glucose
M.Wt	342.30 g mol ⁻¹ (anhydrous)	342.30 g mol ⁻¹ (anhydrous)
	360.31 g mol ⁻¹ (monohydrate)	360.31 g mol ⁻¹ (monohydrate)
M.Formula	C ₁₂ H ₂₂ O ₁₁ (anhydrous)	C ₁₂ H ₂₂ O ₁₁ (anhydrous)
	C ₁₂ H ₂₂ O ₁₁ · H ₂ O (monohydrate)	C ₁₂ H ₂₂ O ₁₁ · H ₂ O (monohydrate)
M. Structure		
Description	A white to off white, crystalline powder	A white, crystalline powder

- Lactose is metabolized to glucose and galactose while, maltose is metabolized to only glucose. Glucose is further metabolized to Glucose-6-Phosphate which in turn undergoes glycolysis for energy production. Thus, both lactose and maltose after complete metabolism result in the end product glucose-6-phosphate which undergoes glycolysis for energy production. Hence, lactose and maltose may have a similar impact on the pharmacokinetics of tigecycline as the end product of their metabolism is the same^{5,6,7}.
- Tigecycline is not extensively metabolized, the main metabolic pathway of tigecycline is glucuronidation. After intravenous administration of [¹⁴C] tigecycline, unchanged drug was the predominant radiolabeled component in serum, urine and feces, with more than half of the radioactivity excreted within 48 h of dosing identified as [¹⁴C] tigecycline^{8,9}.

⁵ Arola H and Tamm A. Metabolism of lactose in the human body. Scand J Gastroenterol Suppl 1994; 202: 21-25. DeMaio,

⁶ Tahara Y, Fukuda M, Yamamoto Y et al. Metabolism of intravenously administered maltose in renal tubules in humans. Am J Clin Nutr 1990; 52(4): 689-693.:

⁷ Holden HM, Rayment I and Thoden JB. Structure and function of enzymes of the Leloir pathway for galactose metabolism. J Biol Chem 2003; 278(45): 43885-43888.

⁸ Hoffmann M, DeMaio W, Jordan RA et al. Metabolism, excretion, and pharmacokinetics of [¹⁴C]tigecycline, a first-in-class glycylcycline antibiotic, after intravenous infusion to healthy male subjects. Drug Metab Dispos 2007; 35(9): 1543-1553.

- Maltose is generally well tolerated and it has no clinically significant interactions with other drugs¹⁰. As discussed above, metabolic and disposition pathway of Tigecycline and maltose are entirely different therefore the possibility of maltose interfering in metabolism of tigecycline is minimal.
- In the in vitro human plasma protein binding study, the free tigecycline and protein bound tigecycline was comparable to reference products and in line with literature values reported for the innovator. These data indicate that maltose containing test product has similar protein binding to that of lactose containing reference product thereby both product can be expected to have similar distribution and elimination characteristics.

The Applicant also claimed that there are no reports or warnings published related to potential drug interaction between maltose and other parenteral drug including Tigecycline. Maltose is used in variety of parenteral formulation (b) (4) for lyophilized product.

Reviewer's Final Assessment: Adequate:

This 505 (b)(2) Application relies for its approval, on FDA's findings of safety and effectiveness for the listed drug. In addition, the NDA includes a biowaiver request for the requirement to conduct a bioavailability/bioequivalence study(ies).

It is noted that the proposed drug product submitted under a 505(b)(2) NDA does not fully satisfy the criteria for a waiver of evidence of in vivo bioavailability under 21 CFR 320.22(b)(1). Under this regulation, a drug product's in vivo bioavailability or bioequivalence may be considered self-evident and a waiver of in vivo studies may be granted if the drug product meets the following criteria:

- It 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 proposed drug product is a parenteral solution for administration by injection, and has the same active ingredient (tigecycline), and has the same dosage form, route of administration and indication as the LD. However, the proposed product and the reference product are different with regard to the inactive ingredients (b) (4).

⁹ Townsend ML, Pound MW and Drew RH. Tigecycline in the treatment of complicated intra-abdominal and complicated skin and skin structure infections. Ther Clin Risk Manag 2007; 3(6): 1059-1070.

¹⁰ Schleis TG. Interference of maltose, icodextrin, galactose, or xylose with some blood glucose monitoring systems. Pharmacotherapy 2007; 27(9): 1313-1321.

maltose monohydrate (proposed) and lactose monohydrate (LD)]. As supported by the additional information [protein binding study, literature, similarity in formulation, pH and osmolality and solubility of tigecycline], the differences in inactive ingredients are not expected to affect the bioavailability of tigecycline in the proposed drug product.

Although, the criteria for a biowaiver under 21 CFR 320.22(b)(1) is not fully met, based on 21 CFR 320.24(b)(6), the FDA can rely on any other approach deemed adequate to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products.

Specifically for NDA 208744, inclusion of (b) (4) maltose monohydrate instead of lactose monohydrate is not expected to have an impact on the disposition of tigecycline from the Applicant's proposed formulation as compared to the reference formulation. Therefore, the Applicant's request for a waiver of the in vivo study for their proposed product, Tigecycline for Injection [50 mg/vial], is granted.

3. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

N/A. Tigecycline for Injection [50 mg/vial] is an orange, clear, sterile solution after reconstitution and dilution; it is intended solely for administration by injection [intravenous infusion]. Since this is a parenteral solution, in-vitro dissolution testing is not applicable.

4. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

The same formulation was used for development and the commercial product. No bridging is needed.



**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACEUTICS**

Reviewer's Assessment and Signature:

A waiver of the in vivo bioequivalence study requirement is granted.
From the Biopharmaceutics perspective, NDA 208744 for Tigecycline for Injection [50 mg/vial] is recommended for **APPROVAL**.

6/03/2016

Om Anand, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Review Concurrence and Signature:

I concur with Dr. Anand's assessment and approval recommendation.

6/03/2016

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Team Leader
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

5. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:**P.2.5 Microbiological Attributes**

- **Container-Closure and Package integrity -**

(b) (4)

Results:

Sample	# Positive/ # Tested
Test Units	0/20
Positive Control	5/5
Test preparation*	6/6

Acceptable

- **Antimicrobial Effectiveness Testing -**

N/A. The subject drug product is a single dose; antimicrobial effectiveness testing is not required.

Acceptable



QUALITY ASSESSMENT



the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

(b) (4)

There were no microbiology deficiencies identified. The submission is recommended for approval on the basis of sterility assurance.

Yuansha Chen, Ph.D.
CDER/OPQ/OPF/DMA/Branch II

**Secondary Review Comments and Concurrence:**

I concur

Nandini Bhattacharya, Ph.D.
CDER/OPQ/OPF/DMA/Branch II
4.25.2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

Pursuant to 21 CFR 25.3 1(a) and 25.15(d), Accord here by claims a categorical exclusion from the requirement of an environmental Impact Analysis statement and states that to the Accord knowledge, no extraordinary circumstances exist.

Under 21 CFR 25.31 (a), a categorical exclusion exists for New Drug Application (NDA).

Accord is requesting FDA to take action by approving NDA for Tigecycline for Injection, USP 50 mg/vial this is an action specified in 21 CFR 25.31(a).

In addition, Accord meets the other requirements of 21 CFR 25.31 (a) because, as stated more completely in Module 1 of this application Tigecycline for Injection, USP 50 mg/vial will be administered at the same dosage level, for the same duration and for the same indication as reference listed drug, TYGACIL® (tigecycline) for Injection; NDA# 021821 of PF PRISM CV.

In addition, Accord is unaware of any other data that would establish that Tigecycline for Injection, USP 50 mg/vial may be toxic to organism in the environment at expected levels of exposure.

On the basis of the foregoing, Accord submits that an Environmental Impact Analysis statement is not required with this application and, therefore, requests that it be categorically excluded from the requirement to submit an Environmental Impact Analysis.

Accord certifies that, it is in compliance with all federal, state and local environmental protection requirements and that it has a certified waste disposal program.

Reviewer's Assessment:

Acceptable

There is no significant increase for use of tigecycline and the applicant declares that it is in compliance with all federal, state and local environmental protection requirements and that it has a certified waste disposal program.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL



QUALITY ASSESSMENT



Reviewer's Assessment and Signature:

Yong Wang

CDER/OPQ/ONDP/NDPI/Branch III

June 30, 2016

Secondary Review Comments and Concurrence: I concur with the Reviewer's assessment as above: Acceptable

Dorota Matecka, Ph.D.; CMC Lead; Branch III; Division of New Drug Products I

July 1, 2016

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

(Attach proposed text)

The following PI draft is based on the amendment dated May, 2006.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TIGECYCLINE FOR INJECTION safely and effectively. See full prescribing information for TIGECYCLINE FOR INJECTION.

TIGECYCLINE for injection for intravenous use
Initial U.S. Approval: 2005

WARNING: ALL-CAUSE MORTALITY

See full prescribing information for complete boxed warning.

All-cause mortality was higher in patients treated with tigecycline for injection 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. Tigecycline for injection should be reserved for use in situations when alternative treatments are not suitable (1.4, 5.1, 5.2, 6.1).

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary name: NA Established name: TIGECYCLINE FOR INJECTION	This section is acceptable since established name is provided. Acceptable
Dosage form, route of administration	Dosage form: FOR INJECTION Route of administration: TIGECYCLINE for injection USP for intravenous use	Dosage form and route of administration are provided. Acceptable
Controlled drug substance symbol (if applicable)	NA	NA
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		

Conclusion: Adequate

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

For Injection: Each single-dose 10 mL glass vial contain 50 mg of tigecycline USP as an orange lyophilized powder for reconstitution.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Dosage form: an orange lyophilized powder for reconstitution	Acceptable
Strengths: in metric system	Strengths: Each single-dose 10 mL glass vial contain 50 mg of Tigecycline	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Each single-dose 10 mL glass vial contain 50 mg of tigecycline USP as an orange lyophilized powder for reconstitution.	The dosage form and color description are provided. However, the word "contain" should be changed to "contains."

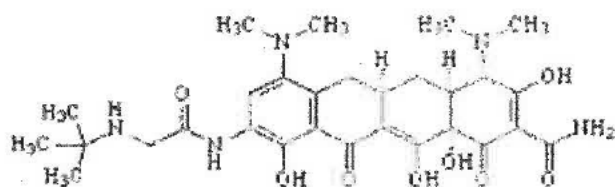
Conclusion: Inadequate
Compared to that of an approved PI for Tygacil (approved on 1/19/2016), the content in Section 3: Dosage Forms and Strengths, is acceptable. However, the following should be communicated to the applicant.

In Section 3: Dosage Forms and Strengths, the word "contain" should be changed to "contains."

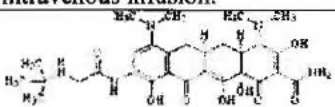
#11: Description (21CFR 201.57(c)(12))

Tigecycline for injection USP^(b) is a tetracycline class antibacterial for intravenous infusion. The chemical name of tigecycline USP is (4S,4aS,5aR,12aS)-9-[2-(tert-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2naphthacene-carboxamide. The empirical formula is C₂₉H₃₉N₅O₈ and the molecular weight is 585.65.

The following represents the chemical structure of tigecycline^{(b) (4)}:



Tigecycline for injection USP^{(b) (4)} is an orange lyophilized powder or cake. Each tigecycline for injection USP^{(b) (4)} vial contains 50 mg tigecycline^{(b) (4)} lyophilized powder for reconstitution for intravenous infusion and 100 mg of maltose^{(b) (4)} monohydrate. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide. The product does not contain preservatives.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Established name: Tigecycline for injection USP	Acceptable
Dosage form and route of administration	Tigecycline for injection ^{(b) (4)} USP ^{(b) (4)} vial contains 50 mg tigecycline ^{(b) (4)} lyophilized powder for reconstitution for intravenous infusion and 100 mg of maltose ^{(b) (4)} monohydrate.	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	NA	NA
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Tigecycline for injection ^{(b) (4)} JSP ^{(b) (4)} vial contains 50 mg tigecycline ^{(b) (4)} lyophilized powder for reconstitution for intravenous infusion and 100 mg of maltose ^{(b) (4)} monohydrate.	Acceptable
Statement of being sterile (if applicable)	N/A	Acceptable
Pharmacological/ therapeutic class	Tigecycline for injection USP ^{(b) (4)} is a tetracycline class antibacterial for intravenous infusion.	Acceptable
Chemical name, structural formula, molecular weight	 Chemical name: (4S,4aS,5aR,12aS)-9-[2-(tert-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2naphthacenecarboxamide Structural formula: C₂₉H₃₉N₅O₈ Molecular weight: 585.65.	Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Tigecycline for injection ^{(b) (4)} USP ^{(b) (4)} is an orange lyophilized powder or cake. Each tigecycline for injection ^{(b) (4)} JSP ^{(b) (4)} vial contains 50 mg tigecycline ^{(b) (4)} lyophilized powder for reconstitution for intravenous infusion and 100 mg of maltose ^{(b) (4)} monohydrate. The pH is adjusted with hydrochloric acid,	Acceptable



QUALITY ASSESSMENT



	and if necessary sodium hydroxide. The product does not contain preservatives.	
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Conclusion:*Acceptable*

Compared to that of an approved PI for Tygacil (approved on 1/19/2016), the content in Section 11: Description, is acceptable.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Tigecycline for injection USP^{(b)(4)} is supplied in a single-dose 10 mL glass vial containing 50 mg tigecycline lyophilized powder for reconstitution.

Supplied:

10 mL - 10 vials/box. NDC 16729-364-68

Prior to reconstitution, tigecycline for injection, USP^{(b)(4)} should be stored at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.] The reconstituted solution of tigecycline for injection USP^{(b)(4)} may be stored at room temperature (not to exceed 25°C/77°F) for up to 24 hours (up to 6 hours in the vial and the remaining time in the intravenous bag) [see *Dosage and Administration* (2.1)].

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Tigecycline for injection USP ^(b) ₍₄₎ supplied in a single-dose 10 mL glass vial containing 50 mg tigecycline USP lyophilized powder for reconstitution.	Inadequate Per DMEPA's recommendation and discussion, the following should be used: "...containing 50 mg of tigecycline as an orange lyophilized powder for reconstitution." Refer to DMEPA's review by D. Myers for more information.
Available units (e.g., bottles of 100 tablets)	10 mL - 10 vials/box.	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC number: NDC 16729-364-68 Shape: Tigecycline for injection USP ^(b) ₍₄₎ supplied in a single-dose 10 mL glass vial.	Compared to that of an approved PI for Tygacil (approved on 1/19/2016), the content in the section of 16 How Supplied/ Storage and Handling is acceptable.
Special handling (e.g., protect from light, do not freeze)	N/A	N/A
Storage conditions	Prior to reconstitution, tigecycline for injection, USP ^(b) ₍₄₎ should be stored at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.] The reconstituted solution of tigecycline for injection ^(b) ₍₄₎ USP ^(b) ₍₄₎ may be stored at room temperature (not to exceed 25°C/77°F) for up to 24 hours (up to 6 hours in the vial and the remaining time in the intravenous bag) [see Dosage and Administration (2.1)].	Compared to that of an approved PI for Tygacil (approved on 1/19/2016), the general content in the section of 16 How Supplied/ Storage and Handling is acceptable from a CMC perspective.

Manufacturer/distributor name listed at the end of PI following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured For: ¹⁰ Accord Healthcare, Inc., 1009, Slater Road, Suite 210-B, Durham, NC 27703, USA. Manufactured By: ¹⁰ Intas Pharmaceuticals Limited, Plot No.: 457, 458, Village – Matoda, Bavla Road, Ta. - Sanand, Dist.- Ahmedabad – 382 210. India.	Acceptable



QUALITY ASSESSMENT

**Conclusion:****Adequate**

Compared to that of an approved PI for Tygacil (approved on 1/19/2016), the content in the section of 16 How Supplied/ Storage and Handling is acceptable. With respect to the comments in Section 16 of How Supplied/Storage and Handling, refer to DMEPA's review by D. Myers for more information.

2. Container and Carton Labeling

1) Immediate Container Label



QUALITY ASSESSMENT



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		
Route of administration (21.CFR 201.100(b)(3))		
Net contents* (21 CFR 201.51(a))		
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
"Rx only" statement per 21 CFR 201.100(b)(1)		
Storage (not required)		
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		
Bar Code per 21 CFR 201.25(c)(2)***		
Name of manufacturer/distributor (21 CFR 201.1)		
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

****For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label**

****Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.**

Conclusion:

Adequate

The proposed immediate container label is adequate from a CMC perspective. Refer to DMEPA’s review by D. Myers for more additional comment.

2) Carton Labeling

(b) (4)



QUALITY ASSESSMENT



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(c)(1)(B), 21 CFR 201.10(g)(2))	Proprietary name: N/A Established name: Tigecycline for Injection USP. The prominence and layout is acceptable compared to that of the RLD.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	50 mg tigecycline per vial	Adequate
Net contents (21 CFR 201.51(a))	50 mg	Adequate
Lot number per 21 CFR 201.18	The sponsor states that space for lot number is provided.	Adequate
Expiration date per 21 CFR 201.17	The sponsor states that space for expiration date is provided along with lot number.	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Each vial contains 100 mg of maltose monohydrate. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide. Contains no preservatives.	Adequate
Sterility Information (if applicable)	N/A	
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	"Rx only" is displayed prominently on the main panel.	Adequate
Storage Conditions	Prior to Reconstitution: Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 16729-364-68 Contains 10 of NDC 16729-364-03	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	A bar code is provided.	Adequate
Name of manufacturer/distributor	Manufactured for: Accord Healthcare, Inc., Durham, NC 27703. Manufactured by: Intas Pharmaceuticals Limited, Ahmedabad-382 210, INDIA Mfg. Lic. No.: G/1026	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Available	Adequate
"Keep out of reach of	N/A	Adequate



QUALITY ASSESSMENT



children" (optional for Rx, required for OTC)		
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Reconstituted Solution must be Further Diluted for I.V. Infusion	Adequate

Conclusion:*Inadequate*

Compared with prescribing information, container label, and carton label of the RLD (Tigcil), the proposed prescribing information, container label, and carton label are acceptable from a CMC perspective. However, per DMEPA's recommendation and discussion, the following should be used in container and carton labels:

(b) (4) should be corrected as "Single Dose Vial."

For more comments of prescribing information, container labels, and carton label, please refer to DMEPA's review by Deborah E. Myers.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: *Inadequate*

The following comments should be communicated to the applicant:

In Section 3: Dosage Forms and Strengths, the word "contain" should be changed to "contains."

With respect to the comments from DMEPA, refer to Ms. D. Myer's reviews dated March 22, 2016 for more information and comments.

Note the labeling will be reevaluated after resubmission of this NDA.

Yong Wang

CDER/OPQ/ONDP/NDP1/Branch III

June 30, 2016

Secondary Review Comments and Concurrence: I concur

Dorota Matecka, Ph.D.; CMC Lead; Branch III; Division of New Drug Products I
July 1, 2016



II. List of Deficiencies To Be Communicated

Product Quality Comments to be included in the CR letter:

8. 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.
9. 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. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.
10. 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.
11. Please 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.
12. Your application includes a Comparability Protocol that provides (b) (4).
(b) (4)
Since the information currently provided for the drug substance is inadequate due to deficiencies in DMF (b) (4), the proposed Comparability Protocol cannot be evaluated at this time and should be included for review in the resubmitted NDA.

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments

		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability, Impurities	Formulation, Process parameters Raw materials Container closure	L	Deficient DMF for tigecycline <i>Insufficient stability data for DP</i>	Unacceptable	
Uniformity of Dose	Process parameters	L	Adequate in process controls	Acceptable	
Reconstitution time	Formulation, Process parameters Raw materials	M	(b) (4)	Acceptable	
Leachable (b) (4)	Container closure	L	Powder for injection; extractable study results <i>not provided</i>	Unacceptable	
Sterility	Process parameters	H		Acceptable	
Particulate matter	Formulation Process parameters	M	Release and stability testing per USP <788>	Acceptable	
Drug substance manufacturing and testing facility	GMP status and performance of the quality system	H		(b) (4)	

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

/s/

MELISSA V CHHANGTE
01/25/2018