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APPLICATION NUMBER:

208744Orig1s000

SUMMARY REVIEW

Combined Cross-Discipline Team Leader and Division Director Review

Date	(electronic stamp)
From	Dorota Matecka PhD; Sumathi Nambiar MD MPH
Subject	Cross-Discipline Team Leader and Division Director Review
NDA #	208744 Class 2 Resubmission
Applicant	Accord Healthcare Inc.
Date of Submission	July 18, 2017
PDUFA Goal Date	January 18, 2018
Proprietary Name / Established (USAN) names	Tigecycline for Injection* (tigecycline)
Dosage forms/Strength	Powder for injection, 50 mg/vial
Proposed Indication(s)	For the following indications in adults: <ol style="list-style-type: none"> 1. Complicated Intra-abdominal Infections 2. Complicated Skin and Skin Structure Infections 3. Community-Acquired Bacterial Pneumonia
Regulatory Action:	Approval

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

Material Reviewed/Consulted	Names of Discipline Reviewers
Action Package including:	
Pharmacology Toxicology Review	Terry Miller PhD
Product Quality Application Technical Lead	Dorota Matecka PhD
Medical Officer Review	Rama Kapoor MD
Clinical Microbiology Review	Kerian Grande Roche PhD
Clinical Pharmacology Review	Zhixia (Grace) Yan PhD
Division of Risk Management (DRISK) Review	Naomi Redd PharmD
Division of Medication Errors Prevention and Analysis (DMEPA) Review	Deborah Myers RPh MBA

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 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 the Agency's 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 drug, a biowaiver for conducting in-vivo bioequivalence studies was requested by the Applicant.

2. Background

This NDA, originally submitted on September 30, 2015, was issued a complete response (CR) letter on July 22, 2016 due to several Product Quality related deficiencies, including the unacceptable status of the drug substance manufacturing facility. The first NDA resubmission dated May 26, 2017 was deemed incomplete due to the continued inadequate status of DMF (b) (4) referenced in the NDA for tigecycline drug substance. The current NDA resubmission dated July 18, 2017 includes responses to the Product Quality deficiencies included in the CR letter and no other changes have been proposed. Most of the reviewers found this NDA acceptable in the first review cycle, as described in their respective reviews of the original NDA and memos filed in DARRTS for the NDA resubmission. Therefore, the current review focuses mainly on the assessment of the responses to the Product Quality issues.

3. Product Quality

The Product Quality review team included the following reviewers from the Office of Pharmaceutical Quality (OPQ): Dr. Yong Wang (Drug Product), and Dr. Jonathan Swoboda (Facilities), Dr. Haripada Sarker (Drug Substance).

The OPQ review of this resubmission focused primarily on the responses to the product quality deficiencies identified in the first review cycle. 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 reviewed and found acceptable. Also, the DMF referenced for the drug substance, which was recently reviewed for another application in CDER, has been found adequate to support the current NDA. In addition, the Comparability Protocol included in the current NDA (b) (4) was revised (b) (4), and found acceptable. Furthermore, 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 all facilities responsible for manufacturing the drug product and the drug substance for this NDA.

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 is recommended for approval from the Product Quality perspective (refer to OPQ review dated January 10, 2018, in Panorama).

4. Other Relevant Regulatory Issues

The listed drug (Tygacil (tigecycline) for Injection, 50 mg/vial, NDA 21821) 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. 9,694,078 - Expiry Date: March 13, 2016

Accord Pharmaceuticals Inc. submitted Paragraph IV Certification for patents 7879828; 8372995; and 8975242 in the initial NDA submission.

On January 21, 2016, the Applicant certified 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).

The NDA was further amended on March 28, 2016 with a Paragraph IV Certification for additional Patent No. 9254328, which had not been listed in the Orange Book at the time of NDA submission.

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

On August 4, 2017, the Applicant resubmitted Paragraph IV Certification for the previously listed patents 7879828, 8372995, 8975242 and 9254328, and for a new US patent 9694078.

On August 29, 2017, the Applicant informed the Agency that settlement agreement has been reached between Patent Holder and the Applicant, and submitted a copy of Stipulation of Dismissal issued by the United States District Court for the District of Delaware. In a subsequent amendment dated December 13, 2017, the Applicant also stated that no law suit was brought against Accord Healthcare Inc. regarding the new patent 9694078.

5. Labeling

No trade name was proposed for the drug product. Labeling revisions and recommendations provided by several disciplines including DMEPA and DRISK have been incorporated in labeling.

The proposed tigecycline formulation proposed via this NDA contains maltose (instead of lactose present in the listed drug). Products containing maltose can interfere with the readings

of blood glucose monitors which use glucose monitoring strips containing the enzyme glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ). There are other approved drug products on the market that contain maltose as an excipient, and contain the risk of interference with blood glucose reading when test strips that rely GDH-PQQ are used. For all these products the risks are included in labeling, including Boxed Warnings, Warnings and Precautions, and Drug-Device interactions. Extraneal, a drug used in an ambulatory care setting for peritoneal dialysis, also has a REMS with elements to assure safe use (ETASU) due to several reports postmarketing reports of hypoglycemia.

The Applicant has not submitted a REMS in the NDA but included the following statement in a Boxed Warning of the package insert: *“This formulation of Tigecycline for injection contains maltose and may result in falsely elevated glucose readings leading to unrecognized hypoglycemia or inappropriate insulin administration. Glucose testing methods that do not react with maltose should be used when patients are receiving this formulation of tigecycline (2.4, 5.3).”* DRISK and DAIP agreed that a REMS was not necessary for this application because this product will primarily be used in an inpatient setting, the Boxed Warning adequately describes the risk and includes the mitigation strategy, and both container and carton labels include “Each vial contains 100 mg maltose monohydrate: see Boxed Warning”. In addition, the glucose test strips with GDH-PQQ are no longer used in hospitals (b) (4) (refer to the Clinical and DRISK reviews in DARRTS dated December 8, 2017 and December 21, 2017, respectively).

All other recommended changes were agreed to and incorporated by the Applicant in the package insert, and the respective carton and container labels.

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/s/

SUMATHI NAMBIAR
01/15/2018