CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208744Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	208744
PDUFA Goal Date	January 18, 2018
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Reviewer Name(s)	Naomi Redd, Pharm.D.
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Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	December 21, 2017
Subject	Evaluation of the Need for a REMS
Established Name	Tigecycline
Trade Name	Tigecycline
Name of Applicant	Accord Healthcare
Therapeutic class	Glycylcycline antibiotics
Formulation	50mg/ml vial
Dosing Regimen	initial dose of 100 mg, followed by 50mg every 12 hours administered intravenously (IV) over 30 to 60 minutes for 7 to 14 days

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for tigecycline is necessary to ensure the benefits outweigh its risks. Accord Healthcare submitted a 505(b)-2 NDA 208744 for tigecycline with the same indication as the Reference Listed Drug (RLD) for Tygacil which includes the treatment of complicated skin and soft tissue infections, intra-abdominal infections, and community-acquired bacterial pneumonia. This applicant's formulation of tigecycline has maltose as an excipient. The RLD, and other generic formulations of tigecycline do not contain maltose.

Products containing maltose can interfere with glucose readings if glucose monitors use non-specific glucose monitoring strips that rely on the enzyme glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ). This interference may result in falsely elevated blood glucose readings, which in turn may lead to inappropriate insulin administration that causes hypoglycemia. (b) (4) [redacted]. These strips are no longer available in hospitals, which is the primary setting in which tigecycline will be administered.

The applicant did not submit a REMS with this application, but included the potential risk of unrecognized hypoglycemia or inappropriate insulin administration if non-specific glucose monitors are used in the Boxed Warning.

DRISK and DAIP agree that a REMS is not necessary for tigecycline to ensure the benefits outweigh the risks because this product will primarily be used in an in-patient setting, and that the glucose test strips with GDH-PQQ are no longer used in hospitals (b) (4) [redacted]

1 Introduction

This review by the DRISK evaluates whether a REMS for tigecycline is necessary to ensure the benefits outweigh its risks. Accord Healthcare submitted a 505(b)-2 NDA 208744 for tigecycline with the same indication as the RLD for Tygacil which includes the treatment of complicated skin and soft tissue infections, intra-abdominal infections, and community-acquired bacterial pneumonia. Accord's tigecycline for injection has been determined to be pharmaceutically equivalent under a separate review. However, this applicant's formulation of tigecycline has maltose as an excipient which may present the risk of unrecognized hypoglycemia. This interference may occur when glucose test strips with the enzyme, glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) is used to monitor blood glucose. The reagent in these testing strips may present a falsely elevated blood glucose result, which in turn may result in in appropriate insulin administration, leading to hypoglycemia. The RLD does not have maltose as an excipient. The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Tigecycline is a member of the glycylcycline class of antibiotics; a subclass of the tetracyclines. Glycylclines prevent bacterial growth by inhibiting protein synthesis. The RLD, Tygacil, held by Pfizer, was approved in 2013 to treat complicated skin and skin structure infections (cSSSI), complicated intra-abdominal infections (cIAI), and community-acquired bacterial pneumonia (CABP) at an initial dose of 100 mg, followed by 50mg every 12 hours administered intravenously (IV) over 30 to 60 minutes for 7 to 14 days in a hospital setting. Accord Healthcare submitted this NDA as a 505(b)(2) application, and requested a waiver of in-vivo bioequivalence requirement for tigecycline injection in accordance with 21CFR.320.22(b)(1), and thus is not characterized as an NME. This product is similar to the RLD in that the active ingredient and route of administration, dose and indications.[a,b] The proposed drug product is a new formulation in that it contains maltose instead of lactose (b) (4).

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history relevant to this review:

- 09/30/2015: NDA 208744 505(b)(2) submission for tigecycline 50 mg/vial received
- 07/22/2016: Complete Response (CR) letter sent to the Applicant due to deficiencies in chemistry manufacturing controls for the drug substances
- 07/21/2017: Class 2 resubmission to CR acknowledged and complete
- 01/18/2018: PDUFA date

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Complicated skin and skin structure infections, intra-abdominal infections and community-acquired bacterial pneumonia are challenging to treat due to the presence of multi-microbial strains, the high potential for resistance if left treated improperly, and comorbid complications that may result in death. Many of these infections primarily occur in the inpatient setting and are treated based on approaches that combine broad spectrum coverage to effectively inhibit growth and kill microbial strains.[c,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

There are a wide variety of treatment options for each of the above indications which include: cephalosporins, fluoroquinolones (ciprofloxacin), as well as other broad spectrum antibiotics such as linezolid, piperacillin-tazobactam, and vancomycin. Please see the clinical review[1] written by Dr. Dimitri Iarikov submitted in DARRTS June 24, 2016 for more information. Tigecycline is marketed in the United States as Tygacil under NDA 21821 by Pfizer, Inc, as well as other generic tigecycline products.

4 Benefit Assessment

The Applicant did not submit any new clinical information with this NDA. This 505(b)(2) NDA application for tigecycline relies on FDA's previous findings of safety and effectiveness for the RLD Tygacil, held by Pfizer, approved in 2013 to treat cSSSI, cIAI, and CABP approved in 2013.

5 Risk Assessment & Safe-Use Conditions

Tygacil currently has a Boxed Warning for all-cause mortality being higher in patients treated with Tygacil, and should be reserved for use in situations when alternative treatments are not suitable.

As per the clinical review written by Dr. Iarikov, tigecycline remains a viable treatment option for the approved indications. However, the (b) (4) maltose with this formulation presents a safety concern that is not present with the RLD, which contains lactulose (b) (4). Maltose can interfere with the readings of some blood glucose test strips resulting in falsely elevated glucose levels which may lead to unrecognized hypoglycemia, or, inappropriate insulin administration which could also lead to hypoglycemia.[1] The interference may occur when glucose test strips with a reacting agent, glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidodreductase are used. These test strips or monitors cannot distinguish between glucose and non-glucose sugars such as maltose, galactose, and xylose.

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. Appendix 1 provides a listing of currently approved drugs with the amount of maltose in the drug product, as well as how this information is labeled in regards to the risk of interference with blood glucose testing and unrecognized hypoglycemia. All of these drugs communicate this risk through labeling. Some of these drug products communicate the risk in Boxed Warnings, Warnings and Precautions, and Drug-Device interactions. Extraneal, a drug used in an ambulatory care setting for peritoneal dialysis, in addition to containing (b) (4) maltose in its formulation as compared to other drugs in this appendix, also has a REMS with elements to assure safe use (ETASU) due to several reports postmarketing reports of hypoglycemia (See section 8.0 for details on the Extraneal REMS)

6 Expected Postmarket Use

As noted above, tigecycline is expected to be given in an inpatient setting under the supervision and monitoring of healthcare providers.

7 Risk Management Activities Proposed by the Applicant

The Applicant proposed including the risk of unrecognized hypoglycemia in the Boxed Warning. There were no other measures proposed by the Applicant to mitigate this risk.

8 Discussion of Need for a REMS

The risk associated with this product is a drug-device interaction that may occur when glucose test strips with glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) is used to monitor blood glucose. The reagent in these testing strips may present a falsely elevated blood glucose result, which in turn may result in in appropriate insulin administration that could result in hypoglycemia.

The other approved tigecycline products contain lactulose, and are not associated with this risk.

In 2005, the FDA sent out the alert of false glucose results with point-of-care testing. This communication was updated in 2009, with more detailed information on the importance of using specific testing methods (glucose meters and strips) not affected by the presence of maltose, and to review prescribing information of products that contain maltose, xylose, or galactose.[2] This communication also contained a preliminary list of drug products approved at that time with maltose as an ingredient. Please see the Appendix in this review with further detailed information on these products.

In 2008, there were 18 domestic cases of hypoglycemic adverse events reported to the FDA associated with Extraneal (icodextrin) use. In seven of these cases, health care providers used monitors that relied on GDH-PQQ- or GDO-containing test strips to obtain blood glucose readings. These events occurred in a variety of settings including a post-anesthesia care unit, ICU, a general care hospital unit, emergency department (ED), and one case in which paramedics were evaluating a patient at home. Serious outcomes were reported in several of these cases including hypoglycemic coma, persistent vegetative state, and death due to treating what was thought to be a high blood glucose level.[3]

In March, 2011 the Extraneal REMS with elements to assure safe use (ETASU) was approved to address the risk of hypoglycemia resulting from inappropriate insulin therapy from blood glucose results from glucose monitors that use GDH-PQQ.

The goal of the Extraneal REMS is to mitigate the risk of morbidity and mortality associated with the use of non-specific glucose monitors and test strips in patients using Extraneal by:

- Informing the dialysis clinic staff managing the patient's treatment (such as peritoneal dialysis nurses) about the drug-device interaction and the potential for falsely elevated blood glucose readings in patients using Extraneal.
- Informing patients of the drug-device interaction and the need to alert health care providers of this interaction whenever they receive treatment outside of a dialysis clinic.

The REMS elements include:

- Medication Guide (MG)

- ETASU – Extraneal will only be dispensed to patients with documentation of safe use conditions including specially trained peritoneal dialysis staff and peritoneal dialysis clinics and hospitals
- Implementation system

When evaluating the risk:benefit analysis for this NDA of tigecycline, the possible need for a REMS was discussed with the review division, and compared to the REMS for Extraneal as a potential risk mitigation beyond labeling with a Boxed Warning.

As mentioned previously, the risk of unrecognized hypoglycemia is a result of using glucometers and test strips that rely on the reagent GDH-PQQ. (b) (4)

(b) (4)

The DAIP review states that tigecycline is administered daily up to 14 days in patients with severe infections and the product will be primarily used in an inpatient setting. [5] Labeling also includes the following as a box warning, All-*cause mortality was higher in patients treated with tigecycline 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*. DRISK and DAIP agree that a REMS is not necessary for tigecycline to ensure the benefits outweigh the risks because this product , will primarily be used in an in-patient setting and as per labeling should be reserved for when alternative treatments are not

available, and that the glucose test strips with GDH-PQQ are no longer used in hospitals (b) (4)

The team agreed that including the information in the Boxed Warning: "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"[6] as well as on the face of the tigecycline package: "contains 100 mg maltose (b) (4) See Boxed Warning"[7] provides a readily available communication method at the time of dispensing with the need to see monitoring parameters via the label if this NDA for tigecycline is to be used.

9 Conclusion & Recommendations

DRISK and DAIP agree that a REMS is not necessary for tigecycline to ensure the benefits outweigh the risks because this product will primarily be used in an in-patient setting, and that the glucose test strips and monitors that reply on the enzyme GDH-PQQ are no longer used in hospitals (b) (4)

10 Appendix

United States drug products that may interfere with GDH-PQQ based glucose monitoring systems

Trade Name	Generic Name	Sugar and Sugar concentration	Labeling for Blood Glucose Testing Interference/Falsely elevated hyperglycemia
Octagam 5% and 10%[8] (approved 2004)	Immune Globulin Intravenous (Human)	Maltose 100mg/ml	5.3 Blood Glucose Testing: some types of blood glucose testing systems (for example, those based on the GDH-PQQ methods) falsely interpret the maltose contained in Octagam liquid as glucose. This has resulted in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life-threatening hypoglycemia.
WinRho SDF liquid[9] (approved 1995)	Rho(D) Immune Globulin Intravenous (Human)	Maltose 10%	Warnings – false high blood glucose levels; Maltose in IVIG products has been shown to give falsely high blood glucose levels in certain types of blood glucose testing systems (for example by systems based on GDH-PQQ methods)
HepaGamB[10] (approved 2006)	Hepatitis B Immune Globulin Intravenous (human)	Maltose 10%	7.3 – Drug-Laboratory Interactions: Maltose in HepaGam B may interfere with non-glucose specific blood testing systems
Orencia[11] (approved: 2005)	Abatacept for intravenous administration	Maltose – 500mg	7.3 – Drug-(b) (4) Interactions: when receiving Orencia through IV administration, patients that require blood glucose monitoring should be advised to consider methods that do not react with maltose
CNJ-016, Vaccinia Immune Globulin Intravenous[12] (approved 2005)	Immune Globulin Intravenous (human)	Maltose 10%	Boxed Warning, and Warnings and precautions (5.3) – added 7/2009: Blood glucose measurement in patients receiving Vaccinia Immune Globulin Intravenous (Human) must be done with a glucose-specific method (monitor and test strips) to avoid interference by maltose.
Extraneal[13] (initial approval 2002; REMS approval 2011)	Icodextrin (Peritoneal Dialysis solution)	Icodextrin – 7.5gm/100ml	ETASU REMS, Boxed Warning: unrecognized hypoglycemia resulting from drug-device interaction
Tigecycline[6]	Tigecycline	Maltose – 100mg/ml	Boxed warning: 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 (b) (4) 5.3)*

11 References

[1] Iarikov D. NDA 208744, 505(b)(2) Tigecycline for injection Clinical Review. June 24, 2016

[2] Important safety information on interference with blood glucose measurement following use of parenteral maltose /parental galactose/oral xylose-containing products. Accessed Dec 15, 2017. https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm154213.htm

[3] https://www.ismp.org/newsletters/acutecare/articles/20080619.asp

[4] Harris S. NDA 21321/Orig-1 S-419 Extraneal 6th year REMS assessment.

[5] Kapoor R. Medical Officer's Memorandum on review of Class 2 resubmission to a complete response letter for NDA 208744, December 8, 2017

[6] Tigecycline NDA 208744 Draft labeling, November 8, 2017

[7] Myers D. NDA 208744 Review of Revised Label and Labeling, Division of Medication Error Prevention and Analysis, November 1, 2017

[8] Octagam U.S. Prescribing Information, September 2015

[9] WinRho U.S. Prescribing Information, December 2009

[10] HepaGam B U.S. Prescribing Information, August 2016

[11] Orencia U.S. Prescribing Information, June 2017

[12] CNJ-016, Vaccinia Immune Globulin Intravenous, January 2010

[13] Extraneal U.S. Prescribing Information, December 2016

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