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*APPLICATION NUMBER:*

**2087440rig1s000**

**NON-CLINICAL REVIEW(S)**

**Memo to the Division File**

NDA 208744 Resubmission/Class 2, Submitted 7/18/2017

Tigecycline for Injection (Applicant: Accord Healthcare Inc., USA)

From: Terry J. Miller, Ph.D., Pharmacology/Toxicology Supervisor, DAIP

To: Deepak Aggarwal, M.S., Regulatory Project Manager

Date: December 17, 2017

**Recommendations:**

Pharmacology/Toxicology has no objection to the approval of NDA 208744 for Tigecycline for Injection.

The Applicant referenced the FDA approved product labeling for the Reference Listed Drug (RLD) TYGACIL® (tigecycline) for Injection (Pfizer Inc.) and modified the labeling to include PLLR compliant language in Section 8. The Applicant's proposed PLLR changes to Section 8 are acceptable from a pharmacology/toxicology perspective. The remaining pharmacology/toxicology relevant sections of the Applicant's proposed labeling appear consistent with the latest drug product labeling for the RLD Tygacil®.

**Background:**

The Applicant, Accord Healthcare Inc., submitted a Class 2 Resubmission of a 505(b)(2) NDA application for Tigecycline for Injection on 7/18/2017, after receiving a Complete Response from the Division for product quality deficiencies in their original NDA submitted on 09/30/2015 (communication in DARRTS 07/22/2016). The Applicant's amendment containing their response to the Division's Complete Response communication was deemed incomplete as there remained unresolved product quality concerns (communication in DARRTS 06/27/2017). In the current 505(b)(2) NDA resubmission, the Applicant did not submit any new toxicology or pharmacology data for review. There were no new excipients, degradation products or other chemistry issues relevant to pharmacology/toxicology that required evaluation by the nonclinical review team.

The Applicant has updated the package insert to be compliant with PLR labeling requirements, including PLLR format, following the Division's suggestions in prior labeling negotiations (communication in DARRTS 6/22/2016). The Applicant's proposed edits to the pharmacology/toxicology relevant sections of the labeling appear acceptable. The remaining pharmacology/toxicology relevant sections of the Applicant's proposed labeling appear consistent with the latest drug product labeling for the RLD Tygacil®.

The Applicant's proposed labeling for Section 8 (Sections 8.1 and 8.2) now reads:

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Tigecycline may cause fetal harm [see Warnings and Precautions (5.6)]. There are no adequate studies of tigecycline in pregnant women. At exposures of 5 and 1 times the human exposure in rats and rabbits respectively, there were no teratogenic effects; however, in the rabbit, fetal loss was also observed (see Animal Data).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20% respectively.

#### Data

##### *Animal Data*

Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, <sup>14</sup>C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of intravenous tigecycline during the period of organogenesis was associated with reductions in fetal weights and an increased incidence of skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively (28 mcg·hr/mL and 6 mcg·hr/mL at 12 and 4 mg/kg/day). An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.

### **8.2 Lactation**

#### Risk Summary

There is no information regarding the presence of tigecycline in human milk, the effects on the breast-fed infant, or the effects on milk production. However, in nursing rat pups, there was little or no systemic exposure to tigecycline (*see Data*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tigecycline and any potential adverse effects on the breastfed infant from tigecycline or from the underlying maternal condition.

#### Data

Results from animal studies using <sup>14</sup>C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.

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/s/  
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TERRY J MILLER  
12/18/2017

Memo to the Division File

NDA 208744

Tigecycline

From: Wendelyn Schmidt, Pharmacology/Toxicology Supervisor, DAIP

To: Deepak Aggerwal, Project Manager

Date: February 22, 2016

Background:

The sponsor did not submit any new chemistry, toxicology or pharmacology data to this 505(B)(2) NDA. The PLR label must be updated to a PLLR format. There were no new excipients, degradation products or other chemistry issues raised.

Recommendation: There are no pharmacology/toxicology objections to approval of this NDA. The label will need to be updated as described below.

In the Pregnancy section, the order needs to be changed, a risk summary statement added, and data on the general incidence of birth defects added (as well as data on pregnancy outcomes in aspergillus, if available).

The label formerly read:



The label now reads:

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

There are no adequate (b) (4) studies of tigecycline in pregnant women. (b) (4)

At exposures of 5 and 1 times the human exposure in rats and rabbits respectively, there were no teratogenic effects (see Animal Data).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20% respectively.

#### Animal Data

Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, <sup>14</sup>C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of tigecycline (b) (4) during the period of organogenesis was associated with reductions in fetal weights and an increased incidence of skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively (28 mcg·hr/mL and 6 mcg·hr/mL at 12 and 4 mg/kg/day). An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.

### **8.2 Lactation**

#### Risk Summary

There is no information regarding the presence of tigecycline in human milk, the effects on the breastfed infant, or the effects on milk production. However, in nursing rat pups, there was little or no systemic exposure to tigecycline (see (b) (4)). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tigecycline and any potential adverse effects on the breastfed infant from tigecycline or from the underlying maternal condition.

#### (b) (4) Data

Results from animal studies using <sup>14</sup>C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of

tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.

In the “Overdosage” section, [REDACTED] <sup>(b) (4)</sup> should be deleted (see below).

No specific information is available on the treatment of overdosage with tigecycline. Intravenous administration of [REDACTED] <sup>(b) (4)</sup> tigecycline [REDACTED] <sup>(b) (4)</sup> at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. [REDACTED] <sup>(b) (4)</sup>

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Tigecycline is not removed in significant quantities by hemodialysis.

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WENDELYN J SCHMIDT  
07/01/2016