CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205645Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	205645
Supporting document/s:	14
Applicant's letter date:	July 31, 2013 (Original); May 29, 2015 (Resubmission)
CDER stamp date:	June 10, 2014
Product:	Tigecycline
Indication:	Complicated Intra-abdominal Infections
	Complicated Skin and Skin Structure Infections
	Community-Acquired Bacterial Pneumonia
Applicant:	Fresenius Kabi USA, LLC
Review Division:	Division of Anti-Infective Products
Reviewer:	Tessie P. Alapatt PhD
Supervisor/Team Leader:	Wendelyn Schmidt PhD
Division Director:	Sumathi Nambiar MD MPH
Project Manager:	Carmen DeBellas RPH, PharmD

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1 Executive Summary

1.1 Introduction

Tigecycline is approved for treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia and is currently approved in the US as Tygacil (NDA 021821). The Sponsor is submitting this new drug application (NDA) for its proposed lyophilized tigecycline product utilizing the 505(b)(2) regulatory pathway and seeks the same indications as those listed in the Tygacil labeling. The Sponsor's product contains the same active ingredient, tigecycline, at the same concentration as in the Reference Listed Drug (RLD), and is intended to be administered by the same route and using the same dose and dosing regimen as the RLD. The Sponsor's formulation contains a new excipient, L-arginine instead of lactose monohydrate as a (b) (4) (see Section 2.4 below).

Tigecycline, a glycylcycline, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains.

1.2 Brief Discussion of Nonclinical Findings

The Sponsor has not performed any new nonclinical toxicology, genotoxicity, carcinogenicity, reproductive toxicity, or special toxicity studies with the drug product in support of this application. The general toxicology of tigecycline was extensively characterized as part of the development program for Tygacil, and the Sponsor did not duplicate these studies. No nonclinical toxicology studies for tigecycline were identified in the literature. The only new nonclinical study report submitted was a genotoxicity study (Ames assay) for the process impurity called (b) (4) (see Sections 2.5 and 7 below).

1.3 Recommendations

1.3.1 Approvability: From the pharmacology/toxicology perspective, this NDA can be approved.

1.3.2 Additional Non Clinical Recommendations: There are no Pharm/Tox recommendations.

1.3.3 Labeling: There are no changes to the label.

2 Drug Information

2.1 Drug

CAS Registry Number: 220620-09-7

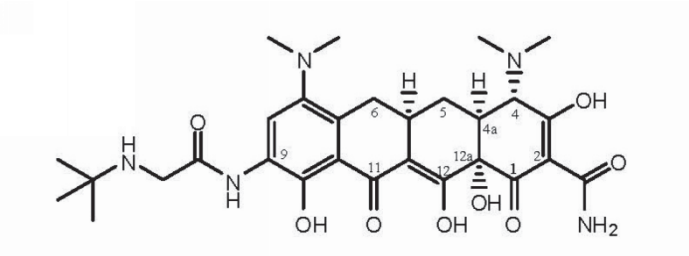
Chemical Names:

Naphthacenecarboxamide, 4,7-bis(dimethylamino)-9-[[[(1,1-dimethylethyl) amino]acetyl] amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11- dioxo-, (4*S*,4a*S*,5a*R*,- 12a*S*)-

(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.

Molecular Formula/Molecular Weight: 585.65

Structure or Biochemical Description:



Pharmacologic Class: Glycylcycline of the Tetracycline family

2.2 Relevant INDs, NDAs, BLAs and DMFs

Tygacil – NDA 02181

2.3 Drug Formulation

Table 3.2.P.1- 2 Component Composition per Unit Dose for Product Code 961110

Strength	50 mg/vial		
Packaging Configuration	(b) (4) mL fill in a 10-mL vial		
Vial	10 mL, (b) (4) Type I Glass vial		
Stopper	(b) (4) rubber stopper		
Seal	20 mm, Flip-off Aluminum crimp seal		
Drug Product Name	**Content (per vial)**	**Function**	**Quality of ingredient**
Tigecycline	50 mg	(b) (4)	N/A
Arginine	82.6 mg		USP
Hydrochloric acid	As needed	pH adjuster	NF
Sodium hydroxide	As needed	pH adjuster	NF
(b) (4)			

2.4 Comments on Novel Excipients

L-Arginine is the novel excipient that is used in this new formulation, which is different from the previous formulation (RLD Tygacil) that contained lactose monohydrate. L-Arginine is present in the amount of 82.6 mg per vial, which amounts to a maximum daily dosing of 247.8 mg. The sponsor justifies this level by stating that Arginine is present in an approved drug product (Aztreonam for injection) at 6.2 g.

2.5 Comments on Impurities/Degradants of Concern

The Division had sent an information request to the sponsor in December 2013 about (b) (4) a process impurity in the final drug product. The concern was that (b) (4) contained a structural alert for mutagenicity and the sponsor was asked to evaluate the mutagenic potential of (b) (4) In response to this the sponsor conducted an Ames assay to evaluate the mutagenicity of (b) (4) (reviewed in Section 7).

The Permitted Daily Exposure (PDE) values for elemental impurities listed in the submission are in compliance with ICH Q3D Step 2B but not with the most recent ICH Q3D Step 4 (finalized on September 2015). Since this application was submitted in May 2015, the PDE values listed are in compliance.

2.7 Regulatory Background

The Sponsor is seeking the same indications as those listed in the approved Tygacil (NDA 02181) labeling for patients 18 years of age and older and is relying upon the Agency's findings of safety and efficacy for Tygacil, to support the approval of this application. The Sponsor is submitting this NDA for the proposed lyophilized tigecycline product utilizing the 505(b)(2) regulatory pathway and has not submitted any new nonclinical data to support its present formulation.

7 Genetic Toxicology

Study title: A mutagenicity test of (b) (4) in Salmonella typhimurium and E. coli
Objective: The test item (b) (4) was examined for the ability to induce gene mutations in tester strains of Salmonella typhimurium and Escherichia coli, as measured by reversion of auxotrophic strains to prototrophy. Experiments were performed both in the absence and presence of metabolic activation, using liver S9 fraction from rats pre-treated with phenobarbitone and betanaphthoflavone. Experiments were performed using the preincubation method.

Study no.:	99310EXT
Sponsor:	(b) (4)
Conducting laboratory and location:	
Date of study initiation:	March 21, 2014
GLP compliance:	No
QA statement:	No
Chemical, lot #, and % purity:	(b) (4) 8125ST05-SG-988-3, 99.0%

Positive Controls used with various tester strains:

Tester strain	Absence of S9	Presence of S9
TA1535	sodium azide 1 µg/plate	2-aminoanthracene 1 µg/plate
TA100	sodium azide 1 µg/plate	2-aminoanthracene 2 µg/plate
TA1537	9-amino-acridine 50 µg/plate	2-aminoanthracene 1 µg/plate
TA98	2-nitrofluorene 2 µg/plate	2-aminoanthracene 2 µg/plate
WP2 *uvr*A	methylmethanesulphonate 500 µg/plate	2-aminoanthracene 20 µg/plate

Methods

Strains:	TA1535, TA1537, TA98, TA100 and WP2 uvrA
Concentrations in definitive study:	See study design table below Main assay I - 5000, 2500, 1250, 625, 313, 156, 78.1 and 39.1 µg/plate Main assay II – 80, 40, 20, 10, 5, 2.5, 1.25, 0.625, 0.313, 0.156 µg/plate
Negative control:	Dimethylsulfoxide (DMSO)
Positive control:	Sodium azide, 9-Aminoacridine, 2-Nitrofluorene, 2-Aminoanthracene, Methylmethanesulphonate (MMS)
Formulation/Vehicle:	Sterile water for injection
Incubation & sampling time:	72 hours at 37°C.

Study Design

The test item was assayed at the following dose levels:

Tester strain	S9	Dose level (µg/plate)
TA1535, TA1537	-	20.0, 10.0, 5.00, 2.50, 1.25, 0.625, 0.313, 0.156
TA100	±	
TA1535, TA1537	+	40.0, 20.0, 10.0, 5.00, 2.50, 1.25, 0.625, 0.313
WP2 *uvr*A	±	
TA98	±	80.0, 40.0, 20.0, 10.0, 5.00, 2.50, 1.25, 0.625

Observation and Results

- The positive and negative controls confirmed the validity of the test conditions and the sensitivity of the test system.

- Main Assay I: Marked toxicity, as indicated by lack of colony growth, lack of background lawn, microcolony formation, thinning of the background lawn and reduction in revertant numbers, was observed with all tester strains at all or almost all dose levels in the absence and presence of S9 metabolism. No precipitation of the test item was observed at the end of the incubation period at any concentration.

- Since at least three different analyzable concentrations (without toxicity) are recommended to evaluate genotoxic activity, a Main Assay II was performed (see study design for doses used).

- Main Assay II: Cytotoxicity (thinning of background lawn) was observed from doses higher than 2.5 µg/plate in all tester strains except *E. Coli*, where cytotoxicity was observed at doses higher than 20 µg/plate. None of the doses caused an increase in the number of reverse mutation colonies above the negative control, with or without metabolic activation.

- Conclusion: (b) (4) does not induce reverse mutation in Salmonella typhimurium or Escherichia coli in the absence or presence of S9 metabolism, under the reported experimental conditions.

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/s/

TESSIE P ALAPATT
11/16/2015

WENDELYN J SCHMIDT
11/16/2015

Memo to the Division File

NDA 205645, sequence #000, Submit date 7/31/2013

Tigecycline for injection, 50 mg/vial, lyophilized powder

From: Wendelyn Schmidt, Pharmacology/Toxicology Supervisor, DAIP

To: Carmen DeBellas, Project Manager, DAIP

Date: September 26, 2013

Background:

The sponsor, Fresenius Kabi, USA LLC, has submitted A NDA for injectable lyophilized tigecycline in a 50 mg vial. The originator consisted of tigecycline and lactose, while this formulation consists of tigecycline and 82.6 mg arginine. The recommended daily dose is 100 mg i.v. followed every 12 hours with another 50 mg i.v. for a total daily dose of 150 mg tigecycline and 247.8 mg arginine. The sponsor noted that the maximum total daily dose of i.v. aztreonam has 6.2 g of arginine. The only pharmacology/ toxicology data submitted to support this NDA is a copy of the package insert label. Thus, the sponsor is relying on the FDA's previous findings of safety and efficacy for tigecycline. Unless the impurity profile of this formulation of tigecycline differs significantly from the previous formulation, there are no pharmacology/toxicology issues with the drug.

Recommendation: From the pharmacology/toxicology perspective, the NDA for tigecycline can be approved. The labeling does not differ from the RLD and there are no changes recommended.

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/s/

WENDELYN J SCHMIDT
09/26/2013