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APPLICATION NUMBER:

208744Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	208744
Submission Date	07/18/2017
Drug	Tigecycline
OCP Reviewer	Zhixia (Grace) Yan Danielsen, Ph.D.
OCP Team Leader	Kellie S. Reynolds, Pharm.D.
OCP Division	DCP4
OND Division	DAIP
Sponsor	Accord Healthcare Inc.
Submission Type	505(b)(2), class 2 resubmission
Formulation	IV Injection, 50 mg/vial
Indication	<p>Tigecycline for injection is a tetracycline-class antibacterial drug indicated in patients 18 years of age and older for:</p> <ul style="list-style-type: none">• Complicated skin and skin structure infections• Complicated intra-abdominal infections• Community-acquired bacterial pneumonia
Dosage and Administration	<ul style="list-style-type: none">• Initial dose of 100 mg, followed by 50 mg every 12 hours administered intravenously over approximately 30 to 60 minutes.• Severe hepatic impairment (Child Pugh C): Initial dose of 100 mg followed by 25 mg every 12 hours.

BACKGROUND

The Applicant submitted a 505(b)(2) New Drug Application (NDA) on 07/18/2017 for Tigecycline for Injection, 50 mg/vial, for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia in patients 18 years of age and older. The strength, route of administration, and dosage regimen of the Applicant's Tigecycline for Injection product are identical to those of the reference listed drug (RLD), TYGACIL[®] (tigecycline) for Injection (NDA 21821; approved in 2005). The formulation of the proposed product substitutes maltose monohydrate for lactose monohydrate contained in TYGACIL (b) (4). A comparison of the proposed product and reference listed drug is presented in Table 1. This NDA is a 505(b)(2) application and as such, relies on the Agency's findings of safety and efficacy for Tigecycline for Injection (TYGACIL[®] - NDA 21821).

Table 1. Formulation Comparison Between the RLD (TYGACIL®) and the Proposed Product (Tigecycline for Injection).

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

This NDA was originally submitted on 09/30/2015. However, the proposed product was not approved due to several deficiencies identified by the FDA product quality team with regards to drug substance, drug product, and manufacturing facilities. Please refer to the Complete Response letter in DARRTS dated 07/22/2016 for more details.

RECOMMENDATION

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed the application. No new clinical pharmacology information was submitted. The Applicant agreed with the Clinical Pharmacology labeling recommendations made in the original NDA review. Thus, this application is acceptable from a clinical pharmacology perspective.

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/s/

ZHIXIA YAN
01/10/2018

KELLIE S REYNOLDS
01/10/2018

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	208744
Submission Date	09/30/2015
Drug	Tigecycline
OCP Reviewer	Zhixia (Grace) Yan, Ph.D.
OCP Team Leader	Seong Jang, Ph.D., Dakshina Chilukuri, Ph.D.
OCP Division	DCP4
OND Division	DAIP
Sponsor	Accord Healthcare Inc.
Submission Type	505(b)(2), resubmission
Formulation	IV Injection, 50 mg/vial
Indication	<p>Tigecycline for injection is a tetracycline-class antibacterial drug indicated in patients 18 years of age and older for:</p> <ul style="list-style-type: none"> • Complicated skin and skin structure infections • Complicated intra-abdominal infections • Community-acquired bacterial pneumonia
Dosage and Administration	<ul style="list-style-type: none"> • Initial dose of 100 mg, followed by 50 mg every 12 hours administered intravenously over approximately 30 to 60 minutes. • Severe hepatic impairment (Child Pugh C): Initial dose of 100 mg followed by 25 mg every 12 hours.

BACKGROUND

Accord Healthcare Inc. submitted a 505(b)(2) New Drug Application (NDA) dated 09/29/2015 for Tigecycline for Injection, 50 mg/vial, which is currently FDA-approved for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia in patients 18 years of age and older. The strength, route of administration, and dosage regimen of the Sponsor's Tigecycline for Injection product are identical to those of the reference listed drug (RLD), TYGACIL® (tigecycline) for Injection (NDA 21821; approved in 2005, manufactured by Wyeth Pharmaceuticals, Inc). The formulation of the proposed product substitutes maltose monohydrate for lactose monohydrate contained in TYGACIL (b) (4). A comparison of the proposed product and reference listed drug is presented in Table 1. This NDA is a 505(b)(2) application and as such, relies on the Agency's findings of safety and efficacy for Tigecycline for Injection (TYGACIL® - NDA 021821).

Table 1. Formulation Comparison Between the RLD (TYGACIL®) and the Proposed Product (Tigecycline for Injection).

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

RECOMMENDATION

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed the application. No new clinical pharmacology information was submitted. Thus, this application is acceptable from a clinical pharmacology perspective.

LABELING COMMENTS/RECOMMENDATIONS

During the filing review of this application, the Clinical Pharmacology Review Team identified the following potential review issue, which was conveyed to the Sponsor on 12/09/2015:

Please submit the relevant references/data to support the following paragraph in the proposed labeling:

Drug Interactions (7), Blood Glucose Testing (7.3)

(b) (4)

methods that do not react with maltose, such as those based on glucose dehydrogenase nicotine adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase (b) (4)

The Sponsor provided the following response to the aforementioned Clinical Pharmacology Information Request on 12/28/2015:

Sponsor's Response: We acknowledge agency's comments, and accordingly we are providing relevant references/data to support above comment.

(b) (4)

Reviewer Comment:

(b) (4)

the addition of a Section 7.3 “Blood Glucose Testing” in the proposed Tigecycline for Injection product labeling appears reasonable. We defer to the Medical Officer for the final decision on the appropriate labeling language to address the risk of unrecognized hypoglycemia associated with the proposed Tigecycline for Injection product due to interference with blood glucose testing.

Clinical Pharmacology Labeling Recommendations for Section 12.3 Pharmacokinetics

We recommend the Sponsor change the proposed labeling as provided below [indicated as underline (additions) and ~~strike through~~ (deletions) in BLUE].

12.3 Pharmacokinetics

The mean pharmacokinetic parameters of tigecycline after single and multiple intravenous doses based on pooled data from clinical pharmacology studies are summarized in Table 3. Intravenous infusions of tigecycline were administered over approximately 30 to 60 minutes.

Table 3. 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 _{max} (mcg/mL) ^c	0.9 (30%)	0.63 (15%)
AUC (mcg•h/mL)	5.19 (36%)	--
AUC _{0-24h} (mcg•h/mL)	--	4.7 (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 (82%)	51 (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

Distribution

The *in vitro* plasma protein binding of tigecycline ranges from approximately 71% to 89% at concentrations observed in clinical studies (0.1 to 1 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.

Following the administration of tigecycline 100 mg followed by 50 mg every 12 hours to 33 healthy volunteers, the tigecycline AUC_{0-12h} (134 mcg•h/mL) in alveolar cells was approximately 78-fold higher than the AUC_{0-12h} in the serum, and the AUC_{0-12h} (2.28 mcg•h/mL) in epithelial lining fluid was approximately 32% higher than the AUC_{0-12h} in serum. The AUC_{0-12h} (1.61 mcg•h/mL) of tigecycline in skin blister fluid was approximately 26% lower than the AUC_{0-12h} in the serum of 10 healthy subjects.

In a single-dose study, tigecycline 100 mg was administered to subjects prior to undergoing elective surgery or medical procedure for tissue extraction. Concentrations at 4 hours after tigecycline administration were higher in gallbladder (38-fold, n=6), lung (3.7-fold, n=5), and colon (2.3-fold, n=6), and lower in synovial fluid (0.58-fold, n=5), and bone (0.35-fold, n=6) relative to serum. The concentration of tigecycline in these tissues after multiple doses has not been studied.

Elimination

Metabolism

Tigecycline is not extensively metabolized. *In vitro* studies with tigecycline using human liver microsomes, liver slices, and hepatocytes led to the formation of only trace amounts of metabolites. In healthy male volunteers receiving ¹⁴C-tigecycline, tigecycline was the primary ¹⁴C-labeled material recovered in urine and feces, but a

glucuronide, an N-acetyl metabolite, and a tigecycline epimer (each at no more than 10% of the administered dose) were also present.

(b) (4) -Excretion

The recovery of total radioactivity in feces and urine following administration of ^{14}C -tigecycline indicates that 59% of the dose is eliminated by biliary/fecal excretion, and 33% is excreted in urine. Approximately 22% of the total dose is excreted as unchanged tigecycline in urine. Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline and its metabolites. Glucuronidation and renal excretion of unchanged tigecycline are secondary routes.

Specific Populations

~~Patients with~~ Hepatic Impairment

In a study comparing 10 patients with mild hepatic impairment (Child Pugh A), 10 patients with moderate hepatic impairment (Child Pugh B), and 5 patients with severe hepatic impairment (Child Pugh C) to 23 age and weight matched healthy control subjects, the single-dose pharmacokinetic disposition of tigecycline was not altered in patients with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25% and the half-life of tigecycline was prolonged by 23% in patients with moderate hepatic impairment (Child Pugh B). Systemic clearance of tigecycline was reduced by 55%, and the half-life of tigecycline was prolonged by 43% in patients with severe hepatic impairment (Child Pugh C). Dosage adjustment is necessary in patients with severe hepatic impairment (Child Pugh C) [*see Use in Specific Populations (8.6) and Dosage and Administration (2.2)*].

~~Patients with~~ Renal Impairment

A single dose study compared 6 subjects with severe renal impairment (creatinine clearance < 30 mL/min), 4 end stage renal disease (ESRD) patients receiving tigecycline 2 hours before hemodialysis, 4 ESRD patients receiving tigecycline 1 hour after hemodialysis, and 6 healthy control subjects. The pharmacokinetic profile of tigecycline was not significantly altered in any of the renally impaired patient groups, nor was tigecycline removed by hemodialysis. No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Geriatric Patients

No significant differences in pharmacokinetics were observed between healthy elderly subjects (n=15, age 65 to 75; n=13, age > 75) and younger subjects (n=18) receiving a single 100 mg dose of tigecycline. Therefore, no dosage adjustment is necessary based on age [see *Use in Specific Populations* (8.5)].

Pediatric Patients

A single-dose safety, tolerability, and pharmacokinetic study of tigecycline in pediatric patients aged 8 to 16 years who recently recovered from infections was conducted. The doses administered were 0.5, 1, or 2 mg/kg. The study showed that for children aged 12 to 16 years (n = 16) a dosage of 50 mg twice daily would likely result in exposures comparable to those observed in adults with the approved dosing regimen. Large variability observed in children aged 8 to 11 years of age (n = 8) required additional study to determine the appropriate dosage.

A subsequent tigecycline dose-finding study was conducted in 8 to 11 year old patients with cIAI, cSSSI, or CABP. The doses of tigecycline studied were 0.75 mg/kg (n = 17), 1 mg/kg (n = 21), and 1.25 mg/kg (n=20). This study showed that for children aged 8 to 11 years, a 1.2 mg/kg dose would likely result in exposures comparable to those observed in adults resulting with the approved dosing regimen [see *Dosage and Administration* (2.3)].

Gender

In a pooled analysis of 38 women and 298 men participating in clinical pharmacology studies, there was no significant difference in the mean ($\pm$ SD) tigecycline clearance between women (20.7 ± 6.5 L/h) and men (22.8 ± 8.7 L/h). Therefore, no dosage adjustment is necessary based on gender.

Race

In a pooled analysis of 73 Asian subjects, 53 Black subjects, 15 Hispanic subjects, 190 White subjects, and 3 subjects classified as “other” participating in clinical pharmacology studies, there was no significant difference in the mean ($\pm$ SD) tigecycline clearance among the Asian subjects (28.8 ± 8.8 L/h), Black subjects (23 ± 7.8 L/h), Hispanic

subjects (24.3 ± 6.5 L/h), White subjects (22.1 ± 8.9 L/h), and “other” subjects (25 ± 4.8 L/h). Therefore, no dosage adjustment is necessary based on race.

Drug Interactions Studies

Digoxin

Tigecycline (100 mg followed by 50 mg every 12 hours) and digoxin (0.5 mg followed by **APPEARS THIS WAY ON ORIGINAL**

0.25 mg, orally, every 24 hours) were co-administered to healthy subjects in a drug interaction study. Tigecycline slightly decreased the $C_{\max}$ of digoxin by 13%, but did not affect the AUC or clearance of digoxin. This small change in $C_{\max}$ did not affect the steady-state pharmacodynamic effects of digoxin as measured by changes in ECG intervals. In addition, digoxin did not affect the pharmacokinetic profile of tigecycline. Therefore, no dosage adjustment of either drug is necessary when tigecycline is administered with digoxin.

Warfarin

Concomitant administration of tigecycline (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single-dose) to healthy subjects resulted in a decrease in clearance of R-warfarin and S-warfarin by 40% and 23%, an increase in $C_{\max}$ by 38% and 43% and an increase in AUC by 68% and 29%, respectively. Tigecycline did not significantly alter the effects of warfarin on INR. In addition, warfarin did not affect the pharmacokinetic profile of tigecycline. However, prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin.

In vitro studies in human liver microsomes indicate that tigecycline does not inhibit metabolism mediated by any of the following 6 cytochrome P450 (CYP) isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. Therefore, tigecycline is not expected to alter the metabolism of drugs metabolized by these enzymes. In addition, because tigecycline is not extensively metabolized, clearance of tigecycline is not expected to be affected by drugs that inhibit or induce the activity of these CYP450 isoforms.

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/s/

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06/21/2016

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06/21/2016
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