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APPLICATION NUMBER:

205436Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

CROSS DISCIPLINARY TEAM LEADER MEMO

Application Type	NDA
Application Number(s)	205435 and 205436
Priority or Standard	Priority
Submit Date(s)	October 18, 2014
Received Date(s)	October 21, 2014
PDUFA Goal Date	June 21, 2014
Division / Office	DAIP/OAP/OND/CDER
Reviewer Name(s)	Shrimant Mishra, M.D., M.P.H.
Review Completion Date	06/09/2014
Established Name	Tedizolid phosphate
(Proposed) Trade Name	Sivextro
Therapeutic Class	Oxazolidinone
Applicant	Cubist Pharmaceuticals
Formulation(s)	Oral and Intravenous
Dosing Regimen	Oral tablet: 200 mg once daily for 6 days Lyophilized powder for intravenous (IV) injection: 200 mg once daily for 6 days
Indication(s)	Acute bacterial skin and skin structure infections
Intended Population(s)	Adults

1. Introduction

This Cross Disciplinary Team Leader Memo concerns the review of NDAs 205435 and 205436- the use of a new molecular entity, the antimicrobial prodrug of the oxazolidinone class known as tedizolid phosphate, for the treatment acute bacterial skin and skin structure infections (ABSSSI). This New Drug Application(s) was submitted on 10/21/2013. It was given a QIDP designation in January 2013 and under the GAIN Act qualified for a priority review. Under the review program established under PDUFA V, the User Fee Goal date was set for June 20th, 2014. An Advisory Committee meeting to discuss the general merits of the application was held on March 31st, 2014. This memo will attempt to highlight the conclusions of the various disciplines involved in the review, and then attempt to synthesize this information in order to provide a recommendation for or against approval. More in depth discussion will be given to discipline specific issues that may have arisen during the course of the review.

Tedizolid phosphate is to be administered as a 200mg dose for six days as either an IV or oral formulation. The oral formulation is highly bioavailable and reportedly needs no dosage adjustment when moving from IV to oral therapy or vice versa. The drug is reported to have a wide spectrum of activity against gram positive organisms that are relevant to the ABSSSI indication, in particular MRSA.

Two pivotal phase 3, randomized, active-controlled, multicenter noninferiority trials were conducted that appeared to have met the prespecified noninferiority criterion for the primary endpoint. Two supportive phase 2 trials, one of which was dose finding, were also conducted. Importantly, the sponsor asserts that tedizolid phosphate has a better safety profile than its class comparator, linezolid, particularly as regards the incidence of myelosuppression, peripheral and optic neuropathy, and drug drug interactions, and has submitted proposed labelling to reflect these claims.

2. Background

There are two issues of note which are useful in understanding the evaluation of this Application. First, the Agency's approach to clinical trials in this indication evolved during the period of this drug's phase 3 development. Because of this, the two phase 3 studies have different primary endpoints. In the first study, study 112, the primary endpoint used (afebrile status and no increase in lesion size at the 48-72 hr. time point) represented a shift from the traditional investigator assessment 7 to 21 days after therapy but differs slightly from the final October 2013 guidance, which incorporated the recommendations of several stakeholders including the Foundation for the National Institutes of Health. This final guidance recommended a primary endpoint of at least a 20 percent reduction in lesion size at the 48-72 hr. visit, and this was used as the primary endpoint for second study, study 113. Thus, due to this, and other reasons including differences in formulation, the studies were not pooled for analysis. Sensitivity analyses were conducted to try and bridge the two studies. Secondly, the Applicant has claimed that tedizolid phosphate is a safer alternative to linezolid, and this is reflected in its proposed labeling. The sponsor's claims are based on its phase 3 findings as well as on several phase 1 and nonclinical studies designed to investigate issues of linezolid-related toxicities such as myelosuppression, peripheral and optic neuropathy, and important drug drug interactions. The merits and conclusions of these studies are discussed in more detail later in the memo.

As expected, each discipline was tasked with evaluating particular issues specific to the application. Issues such as the oral product formulation transition from a disodium salt capsule to a free acid tablet needed particular focus.

3. CMC/Device

The CMC portion of this NDA application was reviewed by Dr. Rajiv Agarwal, and the team leader was Dr. Rapti Madurawe. The OPS Quality Microbiology Reviewers included Dr. Robert Mello and Dr. Bryan Riley. The ONDQA reviewer was Dr. Minerva Hughes (team leader Dr. Angelica Dorantes).

All CMC reviewers found that the study drug was approvable. For both the IV and oral drug product formulations, the CMC review found that there was adequate information to be assured of the identity, strength, purity, and quality of the drug product. Also, both of the OPS Quality Microbiology reviews found the microbial specifications for the drug substance and product to be acceptable. Finally, the ONDQA Biopharmaceutics reviewer found the application for the oral drug product to be acceptable. This section is further divided into a discussion of the oral and intravenous formulations of the drug.

Oral formulation

ONDQA Biopharmaceutics review:

The primary reviewer for this section was Dr. Minerva Hughes and the team leader was Dr. Angelica Dorantes. In this review, Dr. Hughes set out acceptable dissolution method and acceptance criterion for the drug product. The review notes that the proposed commercial product is an immediate release film-coated tablet comprised of the drug substance (200mg tedizolid phosphate), and the excipients microcrystalline cellulose, mannitol, povidone, crospovidone, magnesium stearate (b) (4)

Importantly, the drug substance was first designed as a disodium salt (used in earlier phase 1 and 2 studies) but then was changed to a free acid (used in later phase 2 and 3 studies) in order to improve efficiency in formulation. In a bioavailability study, these two formulations were administered as either a 182 mg free acid **capsule** or 200 mg salt **capsule** in an open label, two treatment, two sequence crossover, PK study in 12 healthy males and females and were shown to be bioequivalent (90% CIs for mean Cmax and AUC values comparing both formulations was contained within the 80% to 125% equivalence range). However, as noted, both formulations were tested as capsules. Later in the development process, the free acid formulation was changed to a tablet. A direct comparison of the two formulations/dosage forms (disodium salt capsule vs. free acid tablet) was not done. However, the tablet free acid formulation was used in both phase 3 studies and has bioavailability data associated with it, and thus some crude comparisons can be made with such data from the prior dosage forms. Such comparisons appeared to be favorable. A food effect study was not conducted with the free acid tablet formulation, and this was concerning given that the results of such trials can be formulation/dosage form dependent. The adequacy of this study in assessing drug substance absorption was assessed by the clinical pharmacology reviewer (see Clinical Pharmacology section).

CMC review

Please note that all figures used in this section were taken from Dr. Agarwal's CMC review

The drug substance manufacturing process was noted to be robust, well controlled, with a high level of impurity control. The (b) (4) drug substance itself was noted to have adequate stability data. Stability data in terms of observed changes in (b) (4) bacterial endotoxins, microbial limits, and impurity levels was found to be acceptable under the conditions tested; a retest period (b) (4) was recommended when the drug substance is stored (b) (4). The drug specification is noted in the table below (taken from Dr. Agarwal's CMC review).

Table 1: Drug Substance Specification- Tedizolid phosphate

Test	Acceptance Criteria	Analytical Procedure
Appearance (b) (4)	White to yellow solid (b) (4)	Visual
		IR (USP <197>)
		HPLC (AP-010)
Assay (b) (4)	NMT (b) (4)	HPLC (AP-010)
		HPLC (AP-010)
Residual Solvents (b) (4)	NMT (b) (4)	UPLC-MS (AP-028)
		GC (AP-011)
		GC (AP-016)
		GC (AP-011 and AP-016)
		GC (AP-029)
		GC (AP-029)
		GC (AP-029)

Table 1: Drug Substance Specification- Tedizolid phosphate; contd.

Test	Acceptance Criteria	Analytical Procedure
Heavy Metals		
(b) (4)	NMT (b) (4)	ICP-OES (AP-012)
	NMT	
	NMT	
	NMT	
	NMT	GF-AAS (AP-013)
	NMT	Chiral HPLC (AP-014)
Water Content	NMT	Karl Fischer (USP <921> Method Ic)
(b) (4)		
Particle Size	NMT (b) (4)	Laser Diffraction (AP-015 and USP <429>)
Residue on Ignition	NMT	USP <281>
Bacterial Endotoxins	NMT	USP <85>
Microbial Limits		USP <61>
Total aerobic microbial count	NMT	
Total yeast and molds count	NMT	

Abbreviations: CFU=colony forming units; EU=Endotoxin Units; GC=Gas Chromatography; GF-AAS=Graphite Furnace-Atomic Absorption Spectroscopy; HPLC=high performance liquid chromatography; ICP-OES=Inductively Coupled Plasma-Optical Emission Spectroscopy; IR=infrared; NMT=not more than; UPLC-MS=Ultra Performance Liquid Chromatography-Mass Spectrometry;

The input of the pharmacology toxicology reviewer, Dr. James Wild, was sought on the acceptance criteria of drug substance impurities. (b) (4)

As is evidenced in the figure above, this was agreed to by the applicant.

The drug product is an oral tablet of 200 mg strength and available as an immediate-release, film coated yellow oval-shaped tablet debossed with "TZD" on the obverse and "200" on the reverse side. The drug product formulation and specifications are noted in the tables below.

Table 2: Drug Product Formulation – Tedizolid phosphate oral form

Component	Quality Standard	Function	200 mg Tablet	
			Weight (mg/unit)	% (w/w)
Tedizolid Phosphate ^a	In-house	Active Ingredient	200	(b) (4)
Microcrystalline Cellulose	NF	(b) (4)		(b) (4)
Mannitol ^b	USP			
Povidone	USP			
Crospovidone	NF			
	(b) (4)			
Magnesium Stearate ^d	NF			(b) (4)
	(b) (4)			
Total Coated Tablet Weight				

Abbreviations: NF=National Formulary; USP=United States Pharmacopeia
 -- not applicable

(b) (4)

Table 3: Drug Product Specification – Tedizolid phosphate oral form

Test	Acceptance Criteria	Analytical Procedure
Appearance	Oval yellow coated tablet debossed with "TZD" on the obverse and "200" on the reverse side	Visual
	(b) (4)	(b) (4)
		FTIR (USP <197> and AP-023)
		HPLC (AP-017)
Assay		HPLC (AP-017)
Degradation Products	(b) (4)	HPLC (AP-017)
	NMT (b) (4)	
	NMT	
	NMT	
Uniformity of Dosage Units by Content Uniformity	Meets USP <905> Requirements	USP <905> and HPLC (AP-017)
Dissolution	NLT (b) (4)/Q in 20 minutes	USP <711> HPLC (AP-018)
	(b) (4)	USP <921>
Microbial Limits		
Total Aerobic Microbial Count	NMT	USP <61>
Total Yeasts and Molds Count	NMT	
<i>Escherichia coli</i>	Absence/g	USP <62>

Abbreviations: CFU=colony forming unit; FTIR=Fourier Transform Infrared Spectrometry; HPLC=high performance liquid chromatography; NLT=not less than; NMT=not more than; Q=quantity

These drug product specifications were found to be in accordance with the ICH Q3B(R) guidance. The drug product tablet is manufactured (b) (4)

The reviewer noted that adequate in-process tests and critical parameters and their acceptance criterion were in place to ensure that the purity, quality and strength of the tablet drug product could be maintained during the manufacturing process. Excipients were tested for conformance with compendial standards. The release acceptance criteria for the excipients were found to be compliant with the appropriate USP/NF monograph; all compendial excipients used in the manufacture of the drug product were listed in the FDA's Inactive Ingredient Guide (IIG) at or below the levels outlined for oral formulation. The only noncompendial ingredient used in the manufacture of tedizolid phosphate tablets, 200 mg, was (b) (4) deemed adequate.

Stability data was analyzed and found to support a 36 month expiration dating period when stored at the labeled conditions of 20°C to 25°C with excursions permitted to 15°C to 30°C. The final recommendation from the Office of Compliance on the compliance to the cGMP involving all facilities pertaining to the drug substance and drug product manufacturing and testing operations was Acceptable.

IV formulation

The drug substance information formulation has already been discussed above. The drug product discussion follows.

Tedizolid phosphate for injection, 200 mg, is a sterile lyophilized powder for injection. Each vial of tedizolid phosphate for injection contains (b) (4) tedizolid phosphate. Following reconstitution of the vial contents with 4 mL of Sterile Water for Injection, a final volume (b) (4) is obtained (b) (4). This volume (b) (4) facilitates withdrawal of 4 mL of the 50 mg/mL tedizolid phosphate solution for full recovery of the label contents (i.e., 200 mg of tedizolid phosphate). The reconstituted dose volume (4 mL) is to be added to 0.9% Sodium Chloride Injection, USP. The formulation of the drug product is highlighted in the figure below.

Table 4: Drug Product Formulation – Tedizolid phosphate intravenous

Component	Quality Standard	Function	Unit Formula
Tedizolid Phosphate	In house	Active Ingredient	(b) (4)
Mannitol	USP	(b) (4)	105 mg
Sodium Hydroxide	USP	(b) (4)	(b) (4)
Hydrochloric Acid	NF	(b) (4)	(b) (4)
(b) (4)	NF	(b) (4)	(b) (4)
Water for Injection ^b	USP	(b) (4)	(b) (4)

Abbreviations: NF=National Formulary; qs=quantity sufficient; USP=United States Pharmacopeia

^bWater for Injection is essentially removed during lyophilization.

Only compendial components are used in the manufacture of the drug product. Each excipient and their amounts present in the formulation are cited in the FDA Inactive Ingredient Database for an injectable and therefore are adequate. There were some initial team discussions of whether the sodium content in the formulation needed to be quantified for section 11 of the labeling (Description section).

(b) (4)

The pH of tedizolid phosphate for injection, reconstituted with 4 mL of Sterile Water for Injection was tested and noted to range from 7.5 to 7.9 for the lots tested on stability. These values are within the proposed acceptance criterion (b) (4). All primary stability lots tested on stability have met the USP requirements for particulate matter, and the dye ingress test was negative.

A 24 hour study was performed to assess the compatibility of tedizolid phosphate for injection with a 250 mL bag of 0.9% Sodium Chloride Injection USP in combination with different IV administration sets that represent those typically found in the clinical setting. No significant change in appearance, particulate matter, assay, impurities, pH, or microbial bioburden in tedizolid phosphate was noted for such reconstituted solutions. The drug product specifications are noted in the table below.

Table 5: Drug Product Specifications- Tedizolid phosphate intravenous IV formulation

Test	Acceptance Criteria	Analytical Procedure
Appearance	White to off-white lyophilized cake in a clear glass vial with stopper, aluminum seal with dark red flip off top	Visual
(b) (4)	(b) (4)	FTIR (USP <197> and AP-024)
		HPLC (AP-020)
Reconstitution Time	NMT (b) (4)	USP <1> and AP-025
Constituted Solutions Completeness Clarity Particulate Matter	Meets USP <1> requirements for constituted solutions	USP <1>
pH of reconstituted solution	(b) (4)	USP <791>
Particulate Matter	(b) (4)	USP <788> Method 2
	NMT (b) (4)	
	NMT (b) (4)	
Assay	(b) (4)	HPLC (AP-020)
Degradation Products	(b) (4)	
	NMT (b) (4)	
	NMT (b) (4)	
	NMT (b) (4)	
	NMT (b) (4)	
Uniformity of Dosage Units by Weight Variation	Meets USP <905> requirements	USP <905>
Loss on Drying	NMT (b) (4)	USP <731> TGA
Sterility	No evidence of microbial growth	USP <71>
Bacterial Endotoxins	NMT (b) (4)	USP <85> Gel Clot

Abbreviations: EU=endotoxin unit; FTIR= Fourier Transform Infrared Spectrometry; HPLC=high performance liquid chromatography; NMT= not more than; TGA=thermogravimetric analysis;

(b) (4)

The specifications for the commercial product are in accordance with the ICH Q3B(R) guidance. Two potential degradation products (b) (4) were identified during the drug substance forced degradation studies and are included in the specification, even though they were not seen during long term and accelerated stability testing in the drug substance or in drug product. Toxicology evaluations for these products were negative. (b) (4)

The manufacturing process steps (unit operations) and processing parameters were evaluated and deemed adequate. In-process control testing was performed to ensure that the manufacture of tedizolid phosphate for injection routinely met product specifications.

In-use reconstitution stability studies were used to analyze appearance, assay, degradation products, reconstitution time, clarity of solution, and visible particulate matter. Stability data supported a 36 month expiration dating period when stored at the labeled conditions of 20°C to 25°C with excursions permitted to 15°C to 30°C.

The final recommendation from the Office of Compliance on the compliance to the cGMP involving all facilities pertaining to the drug product manufacturing and testing operations was “Acceptable.”

4. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology section was reviewed by Dr. Zhixia Yan and her team leader, Dr. Kimberley Bergman. The pharmacometrics review was provided by Dr. Fang Li and his team leader, Dr. Jeffrey Florian. The review included fourteen *in vitro* studies with human biomaterials, sixteen Phase 1 studies evaluating pharmacokinetics of tedizolid phosphate and its active moiety, tedizolid, the two supportive Phase 2 trials, and the two pivotal Phase 3 trials. The findings of the review are summarized below.

Tedizolid phosphate is a oxazolidinone prodrug that is cleaved rapidly by body phosphatases into the active moiety, tedizolid. Given the rapid transformation from prodrug to active drug, the bulk of the review focused on the pharmacokinetics of tedizolid. The following table from Dr. Yan’s review highlights the pharmacokinetics of multiple and single once daily dose of 200mg tedizolid phosphate.

Table 6: Mean (SD) tedizolid pharmacokinetic parameters following single and multiple oral/IV administration of 200 mg once daily tedizolid phosphate in healthy adults.

Pharmacokinetic Parameters of Tedizolid	O		I	
	Single Dose	Steady State	Single Dose	Steady State
AUC ^a (µg·h/mL)	23.8 (6.8)	25.6 (8.4)	26.6 (5.2)	29.2 (6.2)
C _{max} (µg/mL)	2.0 (0.7)	2.2 (0.6)	2.3 (0.6)	3.0 (0.7)
C _{min} (µg/mL)	not applicable	0.44 (0.19)	not applicable	0.36 (0.09)
T _M ^b (h)	2.5 (1.0 – 8.0)	3.5 (1.0 – 6.0)	1.1 (0.9 – 1.5)	1.2 (0.9 - 1.5)
CL or CL/F (L/hr)	6.9 (1.7)	8.4 (2.1)	6.4 (1.2)	5.9 (1.4)

^aAUC is AUC_{0-∞} for single administration and AUC₀₋₂₄ for multiple administration.

^bMedian (minimum, maximum) presented for T_{max}.

Peak plasma tedizolid concentrations are achieved at approximately 3 hours or at 1 hour following oral and IV administration, respectively. The absolute bioavailability was noted to be approximately 91% thus necessitating no further dose adjustment when transitioning between IV and oral administration. Food does not appear to affect the systemic exposure ($AUC_{0-\infty}$) of orally administered tedizolid phosphate exposure. As has already been discussed, following transit to the intestine, the prodrug is cleaved by intestinal alkaline phosphatases into tedizolid. At the intestinal pH, tedizolid phosphate is highly soluble and tedizolid is highly permeable, allowing for the very high absorption/bioavailability of the orally administered dose.

Tedizolid is the most predominant circulating metabolite; it is primarily hepatically metabolized through sulfate conjugation. Following single oral administration of ^{14}C -labeled tedizolid phosphate, 82% of the radioactive dose was recovered in feces and 18% in urine primarily as a non-circulating and microbiologically inactive sulfate conjugate. The majority of elimination was achieved within 96 hours.

Tedizolid has approximately a protein binding level of 80%, and this is not affected by renal and hepatic impairment or hemodialysis. Also, tedizolid has a volume of distribution almost double that of total body water after a single IV dose of 200mg tedizolid phosphate. Tedizolid concentrations in the interstitial space fluid of subcutaneous adipose and skeletal muscle tissue were comparable to free plasma concentrations of tedizolid; free drug exposure was similar in these three compartments.

Tedizolid exhibits linear pharmacokinetics with approximately dose-proportional increase in exposure at tedizolid phosphate doses up to 400 mg (IV) and 1200 mg (oral). Following multiple oral and IV doses of tedizolid phosphate 200 mg once daily in healthy adults, steady state concentrations were achieved within approximately 3 days with a drug accumulation of approximately 30%. The half-life of tedizolid is roughly 12 hours.

Clinical studies demonstrated that no dose adjustment was necessary in the following specific populations: adolescent or elderly patients, males or females, patients with severe renal impairment, patients on hemodialysis, and patients with moderate to severe hepatic impairment. Similarly, age, body weight, BMI, race, ALT, AST, and creatinine clearance did not appear to affect tedizolid pharmacokinetics. Ideal body weight and total bilirubin do appear to affect tedizolid's volume of distribution and clearance (tedizolid clearance increases with ideal body weight but decreases in proportion to total bilirubin, while tedizolid's volume of distribution increases with increasing ideal body weight). However, intersubject variability in clearance and volume of distribution due to these parameters is not expected to be clinically relevant due to the flat exposure-response relationships for efficacy and safety. For example, The change in total bilirubin from 5th percentile to 95th percentile resulted in a 12.4% increase in tedizolid AUC_{ss} . This magnitude of change is not considered to be clinically relevant and the reviewer did not recommend a dose adjustment based on values of ideal body weight and total bilirubin. It should also be noted here that in Phase 3 trials no increase in adverse events were noted in tedizolid phosphate patients with hepatic impairment/disease relative to the comparator.

The reviewer noted that tedizolid's activity appears to be enhanced in the presence of neutrophils. In neutropenic mice, the AUC/MIC ratio needed for bacteriostatic activity was 250, whereas in non neutropenic mice the AUC/MIC target was identified as 15. The etiology of the increased potency in the presence of neutrophils is unclear though tedizolid phosphate appears to have greater intracellular presence than its class counterpart, linezolid. This issue is discussed further in the Clinical Microbiology section.

A tedizolid MIC of 0.5 ug/ml for *Staph.aureus* was proposed by the sponsor, and this was supported by the reviewer's assessment of MIC distributions and clinical PK-PD relationships.

Target attainment analyses along with phase 2/3 clinical data support a 200mg dose.

Exposure analyses highlighted several key findings. Phase 3 trial PK/PD analyses demonstrated a flat exposure-response relationship for the 200mg dose on such efficacy endpoints as clinical response at post treatment (PTE), early clinical response at 48-72 hour, Early Clinical Response with ≥20% decrease in lesion, and microbiological response at post treatment. This corresponds with the flat dose response relationship seen in the dose ranging phase 2 trial that compared the efficacy of a 200mg, 300mg, and 400mg dose in ABSSEI. Safety exposure analyses based on the dose ranging phase 2 study and Phase 3 studies showed that as Day 1 AUC₀₋₂₄ increased, the predicted probability of experiencing any TEAE increased as well. Correspondingly, the incidence of any TEAE increased with increasing tedizolid phosphate dose (200, 300, and 400mg dose). A similar finding was noted specifically with GI AEs as well. There did not appear to be a relationship between drug exposure and decrease in platelets though this should be viewed in the context of a relatively short study 6 day drug regimen. This is in contrast to the findings of a phase 1 study where a dose dependent decrease in platelets was noted in subjects receiving tedizolid phosphate for 21 days (discussed further in Clinical Safety section).

No significant QTc prolongation effects of tedizolid phosphate at 200 mg and 1200 mg were detected in a thorough QT (TQT) study of healthy adults (TR-701-115). The tedizolid concentrations achieved in this study are above those for the predicted worst-case scenario for the 200mg dose (47% increase in C_{max} in adolescents following IV administration relative to adults), and are higher than the concentrations achieved with the maximum multidose testing level (400 mg oral once daily for 21 days).

The pharmacokinetics and safety of tedizolid were evaluated in adolescent (12-17 years of age) subjects (n=20) following a single oral dose (Part A) and a single IV infusion (Part B) of 200 mg tedizolid phosphate. Most PK parameters (i.e., AUC, T_{max}, CL) for tedizolid were similar following a single oral or IV infusion administration of 200 mg tedizolid phosphate between adolescent and adult subjects. However, the C_{max} was 47% higher in adolescent subjects compared to adult subjects (3.85±1.5 vs. 2.62±0.58 µg/ml) following a single IV dose of 200 mg tedizolid phosphate. Due to this potential safety finding and the modest amount of adolescent data available from both this trial and the phase 3 trials (n=1, age=17 years), labeling to include adolescents was not recommended.

The pharmacokinetics of tedizolid were evaluated in subjects with moderate hepatic impairment (Child-Pugh classification B; score of 7–9) and subjects with severe hepatic impairment (Child-Pugh classification C; score of 10–15) versus subjects with normal hepatic function, following a single oral dose of 200 mg tedizolid phosphate under fasted conditions. Generally, tedizolid PK were similar across all groups in this study. The largest differences in tedizolid PK parameters between subjects with hepatic impairment and matched controls were seen in AUC, which was approximately 34% higher in subjects with severe hepatic impairment compared with matched controls, and 22% higher in subjects with moderate hepatic impairment compared with matched controls. Despite these increases, the reviewer stated that this AUC is within the range of exposure observed at doses that demonstrated safety in Phase 1 studies (tedizolid AUC values range from 17.36 to 123.10 µg*hr/ml at 100-1200 mg of single prodrug dose) and Phase 3 studies (mean tedizolid AUC₀₋₂₄ of 22 with a range of 6.57 to 49.86 µg*hr/ml at 200 mg QD prodrug dose). Also the clinical safety reviewer noted that there was no clear disparity in adverse events (serious or otherwise) between subjects with hepatic disease/impairment vs. the comparator or vs. the overall tedizolid population. Thus, no dosage adjustment was recommended for subjects with hepatic impairment.

In vitro oxidative metabolism studies with human liver microsomes indicate tedizolid phosphate and tedizolid are not significant substrates of CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). Similarly, in vitro studies indicate neither tedizolid nor tedizolid phosphate is a substrate or inhibitor of major membrane transporters at usual clinical exposures (OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, BCRP and P-gp).

The relationship between free drug concentrations in plasma and IC₅₀ for MAO inhibition was reviewed. The maximum tedizolid free concentration associated with 200 mg dose regimen is

approximately 20-30% of the IC50 for MAO inhibition, while the maximum linezolid free concentration associated with the recommended dosage of 600 mg twice daily is approximately equal to the IC50 for MAOA inhibition. This apparent lack of MAO inhibition was supported by nonclinical studies (rat tyramine challenge and 5-hydroxytryptophan mouse head twitch [serotonergic model]) which showed no MAO interactions at multiples of up to ~30-fold above the human therapeutic peak tedizolid exposure. Two placebo-controlled crossover studies were conducted to assess the potential of 200 mg/day tedizolid phosphate (at steady state) to enhance pressor responses to oral tyramine or pseudoephedrine. While the pseudoephedrine study appeared to show a lack of pressor enhancement relative to placebo (and when crudely compared to linezolid), the tyramine sensitivity study was slightly less definitive. These studies are discussed in more detail in the Clinical safety section of this review. Overall, however the reviewer concluded that tedizolid did not appear to interact in vivo with adrenergic and serotonergic agents or dietary tyramine at therapeutic exposures.

As has already been discussed, the proposed to-be-marketed formulation of tedizolid phosphate was used in the pivotal Phase 3 Trials, while most in vivo nonclinical and initial Phase 1 and 2 clinical studies used an earlier solid form of the prodrug designated as tedizolid phosphate disodium salt. No direct in vitro or in vivo comparison between the final free acid tablet drug product and the free acid or disodium salt capsules was conducted. In particular, a food effect study was conducted using only the disodium salt capsule. However the reviewer concluded that given 1) the physiochemical properties of the prodrug/active moiety pair (BCS I), 2) bioequivalence between the disodium salt and free acid capsules, and 3) linear PK up to 1200 mg single dose, the findings of the food effect study using capsules would likely reflect what was expected with the to-be-marketed formulation, the free acid tablets (ie., no change in the relevant pharmacodynamics parameter (AUC) was expected with food administration with the 200 mg free acid tablet).

5. Clinical Microbiology

The Microbiology review was performed by Dr. Avery Goodwin; the team leader was Dr. Kerry Snow. Overall, the reviewer deemed the application as approvable.

In vitro studies evaluating tedizolid phosphate's activity against relevant isolates were conducted. Highlighted results include:

Staphylococci

Tedizolid appeared to demonstrate in vitro activity against a wide variety of staphylococcal isolates from the USA and Europe, including VISA, VRSA, methicillin-susceptible coagulase –negative staphylococci (MSCoNS), and methicillin-resistant coagulase –negative staphylococci (MRCoNS). The MIC values ranged from as low as 0.12 mcg/ml to 1.0 mcg/ml.

Streptococci

Tedizolid is active in vitro against relevant streptococci, including *S. pneumonia* (penicillin susceptible, penicillin intermediate and penicillin resistant isolates), beta hemolytic streptococci (MIC90 value of 0.5 mcg/ml), and against the Viridans Group streptococci, (MIC90 was 0.25 mcg/ml).

Enterococci

Tedizolid demonstrated in vitro MIC values that ranged from 0.5 to 1 mcg/mL against vancomycin-susceptible and -resistant *E. faecalis*. Against vancomycin-susceptible and -resistant *E. faecium* tedizolid demonstrated MIC₉₀ values ranging from 0.25-1 mcg/ml.

The distribution of tedizolid susceptibilities in clinical trial isolates appears similar to those of the surveillance isolates.

The data indicate that tedizolid inhibits prokaryotic protein synthesis (prokaryotic translation) but not eukaryotic protein translation. However, TR-700 was shown to inhibit mitochondrial protein synthesis at a dose reported to be 17-26 folds lower than linezolid. Its in vitro activity is mainly considered to be bacteriostatic, other than for *S. pneumonia*, however it does appear to be bactericidal against some isolates, including *Staph. aureus* isolates, in in vivo models. The reason for this discordance is unclear though it could be in part related to the study drug's dependence on granulocytes for its antibacterial activity.

Resistance to oxazolidinone may be chromosomally mediated through mutations in genes encoding the 23S rRNA, or the L3 and L4 ribosomal proteins, and/or it may be plasmid mediated through acquisition of the *cfr* methyltransferase gene. Serial passage studies indicated that in some *E. faecium* and *Staph. aureus* isolates with the chromosomal mutations, there is cross resistance between tedizolid phosphate and linezolid (though generally there were lower MICs for tedizolid). However for *cfr*+ mediated resistance, in some *Staph. aureus* isolated there appears to be retained activity of tedizolid phosphate against these strains. However, this is only ascertained from studies on small numbers of laboratory generated isolates so whether this enhanced activity can be extrapolated to the clinical setting is unknown.

In vitro studies showed no apparent antagonism or synergy between tedizolid and other agents against both gram-positive and gram-negative pathogens. Furthermore, common antifungal agents did not seem to impact tedizolid's in vitro antibacterial activity.

The reviewer evaluated several animal models of infection provided by the Applicant including 1) staphylococcal systemic infections in mice 2) enterococcal systemic infections in mice 3) streptococcal systemic infections in mice 4) MRSA skin and soft tissue infection in mice 5) mouse thigh infection model with MRSA and MSSA 6) rat skin and soft tissue infection 7) lung infection and epithelial lining fluid exposure in mice 8) a neutropenic mouse pneumonia model 9) an *S. aureus* endocarditis model in rabbits 10) and a mouse *Streptococcus pneumonia* model. Efficacy was demonstrated in all models tested.

As discussed in the Clinical Pharmacology section, treatment with tedizolid resulted in a significant increase in antimicrobial activity in the presence of granulocytes compared with animals that were granulocytopenic. In a study conducted by Drusano et al., the efficacy of tedizolid in staphylococcal killing was compared in neutropenic and nonneutropenic mice using a thigh infection model. Examination of both normal and granulocytopenic animals indicated an improvement in the exposure response as a function of the presence of granulocytes. For the granulocytopenic animals, stasis was achieved with a human equivalent dose exposure of approximately 2000, 2100 and 2300 mg administered daily for the 72-, 48-, and 12-hours endpoints, respectively. However, in normal animals stasis was achieved at human-equivalent exposure doses of approximately 100 mg/day at the 24-hour endpoint and less than 100 mg/day at the 48-hour and 72-hour endpoints. Although the mechanism behind this finding is unclear, the reviewer hypothesized that enhanced cellular accumulation of tedizolid and the generation of reactive oxygen species (ROS) during the phagocytosis response may be contributing to tedizolid's enhanced activity in the presence of neutrophils.

In vitro data suggest that tedizolid metabolites have little relevant antimicrobial activity. Also, in a double-blind, placebo-controlled, multiple dose, safety, tolerability and pharmacokinetic study in

healthy Japanese males, there was no sign indicative of microbial flora substitution after multiple IV or oral tedizolid phosphate doses of 200 mg once daily over 7 days.

Together with Clinical Pharmacology, the microbiology reviewer set out the following breakpoints (please see their respective reviews for further discussion; table taken from Dr. Goodwin’s review).

Table 7 Susceptibility Test Interpretive Criteria for Tedizolid phosphate

Pathogen	Minimum Inhibitory Concentrations (µg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (methicillin-resistant and methicillin-susceptible isolates)	≤0.5	1	≥2	≥19	16-18	≤15
<i>Streptococcus pyogenes</i>	≤0.5	-	-	≥18	-	-
<i>Streptococcus agalactiae</i>	≤0.5	-	-	≥18	-	-
<i>Streptococcus anginosus</i> Group*	≤0.25	-	-	≥17	-	-
<i>Enterococcus faecalis</i> vancomycin-susceptible isolates only	≤0.5	-	-	≥19	-	-

6. Nonclinical Pharmacology/Toxicology

This review was performed by Dr. James Wild, with the team leader review performed by Dr. Wendelyn Schmidt. The application was found to be acceptable. Several nonclinical studies are described in other parts of this review, particularly as pertains to nonclinical studies evaluating class specific toxicities. Important findings included:

- 1) Several toxicities were noted at tedizolid phosphate levels higher (and often longer duration) than the planned human exposure. Examples of this included:
 - In safety pharmacology studies (neural, cardiovascular, respiratory, renal and GI) limited tedizolid-related effects occurred only at high doses. These effects included increased hexobarbital-induced sleep time, reduced spontaneous locomotor activity in mice, significantly increased urinary sodium and chloride, and significantly reduced mean gastric volume and mean total gastric acidity.
 - In 2-week, 1-month and/or 3-month studies of oral/IV tedizolid in dogs and rats, hematopoietic (more pronounced in the rat and including decreased RBC, WBC, platelets and bone marrow hypocellularity), gastrointestinal, and injection site

reactions (mostly dogs) were noted. The systemic toxicities were dose and duration dependent, reversible, and occurred at tedizolid plasma exposures between 4 and 10 times higher than those seen in humans.

- In a 1-month rat immunotoxicity study, oral tedizolid was shown to significantly reduce cell counts, splenic T and B cells, IgG titer and IgG mediated plaque formation at TR-700 plasma exposures 4-8 times the human exposure.
- At longer durations and higher doses in the rat, toxicities to the liver (increased liver enzymes and hepatocellular centrilobular degeneration and atrophy), renal tubular degeneration, and reproductive organ degeneration and atrophy in both males and females were observed.

2) Certain linezolid specific toxicities were absent or less prominent with tedizolid phosphate

- A 9-month neurotoxicity study for oral tedizolid administered daily to pigmented rats did not demonstrate peripheral or ocular neuropathy despite approximately exposures 7-8 times the clinical plasma exposure
- Studies evaluating MAO inhibition and serotonin syndrome were essentially negative. A tyramine challenge in rats had no significant effect on mean arterial pressure. Also, data from a study examining serotonergic brain activity in a murine behavioral model suggested no increase in head twitch rates at TR701 exposures equivalent to 30 times the human therapeutic dose.

3) Certain linezolid specific toxicities were also noted with tedizolid phosphate

- Fetal toxicities were noted in embryo-fetal studies, TR-701 was shown to produce fetal developmental toxicities in mice, rats, and rabbits. Fetal developmental effects occurring in mice in the absence of maternal toxicity included reduced fetal weights and an increased incidence of costal cartilage anomalies. In rats, decreased fetal weights and increased skeletal variations including reduced ossification of the sternabrae, vertebrae, and skull were observed at doses associated with maternal toxicity (reduced maternal body weights and mortality). In rabbits, reduced fetal weights but no malformations or variations were observed at doses associated with reduced maternal body weights and abortions. These effects occurred at exposures similar to or below planned human exposures.
- Myelosuppression as described above

Other important findings included :

- ADME findings mimicked those seen in humans.
- Tedizolid phosphate and tedizolid were generally negative for genotoxicity in *in vitro* assays (bacterial reverse mutation (Ames), Chinese hamster lung (CHL) cell chromosomal aberration) and *in vivo* tests (mouse bone marrow micronucleus, rat liver unscheduled DNA synthesis). However, tedizolid was positive in an *in vitro* CHL cell chromosomal aberration assay. Still, the reviewer concluded that the weight of evidence suggested that both drug products had limited potential to be genotoxic in humans.

- Data on mitochondrial toxicity was mixed. *In vitro* experiments using mitochondria isolated from rat heart showed that tedizolid was 20-25 fold more potent than linezolid in inhibiting mitochondrial protein synthesis. However, in another experiment, tedizolid did not distribute into mitochondrial subcellular compartments in isolated macrophages concentrating instead more in phagolysosomes and cytosolic fractions. Neither of these studies is conclusive. From the phase 3 trials it was not readily apparent that mitochondrial toxicity (as evidenced by lactic acidosis, peripheral neuropathy, hepatic steatosis, renal dysfunction, etc.) occurred at any appreciable levels relative to the comparator.
- Fertility studies conducted using a tedizolid exposure 4 to 5 times greater than that of humans (at the proposed dose) were negative
- Slightly more severe signs of local irritation including hemorrhage, focal muscle degeneration with histiocyte infiltration were observed compared to vehicle injection one day and four days after single dose tedizolid phosphate administration by perivascular (PV), intramuscular (IM), and subcutaneous (SC) injections in rabbits. Severe injection site reactions including marked inflammation resulting in swollen and impaired limbs were observed in a 2-week IV toxicology study in dogs, and less severe injection site reactions occurred in some but not all rat IV toxicology studies. Phase 3 trials did not seem to show much difference between the two arms in terms of local tolerability.

Impurities were qualified and checked for toxicity and mutagenicity. One impurity (b) (4) was positive against one strain for mutagenicity in an Ames test (b) (4). Another impurity (b) (4) also demonstrated mutagenicity potential but its acceptance criteria were restricted to levels specified in the “Draft Consensus Guideline ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities and Pharmaceuticals to Limit Potential Carcinogenic Risk.. Carcinogenicity studies were not performed given the proposed short duration of treatment.

7. Clinical/Statistical- Efficacy

It should be noted that the author of this CDTL memo was also the primary efficacy reviewer; the efficacy review itself was evaluated by the Deputy Division Director, Dr. Katherine Laessig. The primary statistical reviewer was Dr. Meg Gamalo, with team leader Dr. Thamban Valappil. There were two randomized, double blind, active controlled, noninferiority phase 3 studies that served as the basis for the efficacy evaluation, Study 112 and 113. The design of both studies generally followed SPA agreements with the Agency (Study 113’s SPA was modified in order to change the primary endpoint from that of the 112 study to the $\geq 20\%$ reduction in lesion size metric). In both studies, subjects were required to have a cellulitis, major abscess, or wound infection lesion with a baseline size of 75 cm² based on erythema alone (Study 112) or based on erythema, induration, or edema (Study 113). For abscesses and wound infection, the shortest distance from the peripheral margin of the wound had to be at least 5 cm. Subjects were also required to have at least a minimum of accompanying local signs (which varied somewhat according to infection type and study) and systemic signs (generally one of lymphadenopathy, fever, leukocytosis/leukopenia, bacteremia). Patients were randomized by geographic region and ABSSI infection type. Subjects were randomized to receive

either 6 days of oral (Study 112) or intravenous/oral (Study 113) tedizolid phosphate or 10 days of oral/intravenous linezolid. Assessment of the primary endpoint took place at the early clinical evaluation (ECE) visit (48-72 hr. visit), while other key assessments of efficacy took place at the end of treatment (EOT) visit (Day 10-11 visit) and post therapy evaluation (PTE) visit (7 to 14 days after EOT).

As has already been noted, the primary endpoint in both studies slightly differed. In study 112, clinical response at the 48-72 hr. visit was considered positive if there was no increase in lesion size and the subject was afebrile at this visit as well the next measurement taken within 24 hours of the visit. In study 113, clinical response was considered positive if the subject had at least a 20% reduction in lesion size. At the later time points, clinical response was assessed either programmatically or through Investigator assessment. At EOT, the programmatic determination of a positive response took into account several variables including lack of fever, decrease from baseline in lesion size, tenderness no more than mild, and lack of concomitant effective antibiotic usage among other things. At PTE, Investigator assessments of clinical success relied on an absence or near absence of local and systemic signs and no new signs requiring treatment for the primary lesion.

In study 112, 332 subjects were randomized to the tedizolid phosphate arm and 335 to the linezolid arm. In study 113, 332 subjects were randomized to the tedizolid phosphate arm and 334 subjects were randomized to the linezolid arm. While subjects were generally matched, the study population was predominantly male and White, with only modest numbers of elderly subjects, pediatric subjects, and diabetic subjects enrolled. Interestingly, there were disproportionately large numbers of subjects (20-36%) with a current or recent history of IV drug use. Cellulitis infections generally made up the majority of infections (40% and 50% of total infections in study 112 and 113, respectively), though there was concern on the part of the reviewer that infection classification may have been erroneous to an uncertain degree due to multiple factors. Median lesion size was between 190cm² in study 112 and 235 cm² in study 113.

Given that these were noninferiority trials, it was important to minimize possible confounding. To that end, prior antimicrobial usage was less than 5% in any arm in either trial and concomitant antimicrobial usage was less than 11% in any arm in either trial (in study 112, it was less than 7%). However, it was noted that the rate of incision and drainage procedures during the study was quite high, averaging just below or just over half the study population in study 112 and 113, respectively. The majority of these procedures occurred just prior to or on Study Day 1.

For study 112, the sponsor noted that their internal audit found 3 sites in violation of cGCP practices. These 3 sites had 18 subjects enrolled in the study. The statistical reviewer elected to exclude these subjects from all analyses associated with the study. However, no real change in the primary endpoint results were noted when these subjects were excluded. Because of this and because the preliminary recommendation from DSI was that sensitivity analyses should be conducted with these subjects excluded (DSI had not had a chance to audit the sites yet), the clinical efficacy reviewer used the original ITT population for analyses.

For both studies, the prespecified noninferiority margin of -10% was met. Please note the table below.

Table 8: Primary Endpoint: Responders at the 48-72 hr. visit, ITT, Study 112 and 113

	Tedizolid Phosphate (N= 332) n (%)	Linezolid (N=335/334) n (%)	Difference, 95% CI
Study 112*			
Responders	264 (79.5%)	266 (79.4%)	0.1 (-6.1, 6.2)
Study 112**			
Responders	259 (78.0%)	255 (76.1%)	1.9 (-4.5, 8.3)
Study 113***			
Responders	283 (85.2 %)	276 (82.6%)	2.6 (-3.0, 8.2)

* The primary endpoint for this study was no increase in lesion size and $T \leq 37.6^\circ$ (oral) at the visit and at next measurement within 24 hours of the visit

** This is a sensitivity analysis to align both studies with the study 113 primary endpoint

***The primary endpoint in this study was at least a $\geq 20\%$ reduction in lesion size compared to baseline

Also notable in the above table is that in a sensitivity analysis where the primary endpoint of study 113 is used to assess response in study 112, there is little change from the original estimate.

For the investigator assessment at PTE, there were also similarly high and comparable rates of clinical success as noted in the table below.

Table 9: Primary Endpoint: Investigator assessment of clinical response at the PTE visit, ITT, Study 112 and 113

	Tedizolid Phosphate (N= 332) n (%)	Linezolid (N=335/334) n (%)	Difference*
Study 112			
Clinical Success	284 (85.5%)	288 (86.0%)	-0.5%
Study 113			
Clinical Success	292 (88.0%)	293 (87.7%)	0.3%

* no prespecified noninferiority margin for this endpoint so CI not shown

Importantly, generally subjects classified as responders at the 48-72 hr. visit did not go on to become failures at later time points though it did occur at a slightly greater level in the tedizolid phosphate arm. Please note the following table from Dr. Gamalo's review.

Table 10: Concordance between ECE at 48-72 hours and Clinical Response at EOT – ITT/ITT* population , Study 112 and 113

Early Clinical Response at 48-72 Hours	Programmatic Determination of Sustained Clinical response at EOT	STUDY 112 (ITT*)		Study 113 (ITT)	
		Tedizolid phosphate	Linezolid	Tedizolid phosphate	Linezolid
		N=323	N=326	N=332	N=334
		n (%)	n (%)	n (%)	n (%)
Responder	Clinical Success	224 (87.5)	236 (91.5)	258 (91.2)	260 (94.2)
	Clinical failure	24 (9.4)	16 (6.2)	18 (6.4)	10 (3.6)
	Indeterminate	8 (3.1)	6 (2.3)	7 (2.5)	6 (2.2)
Nonresponder	Clinical Success	20 (74.1)	16 (45.7)	30 (68.2)	32 (72.7)
	Clinical failure	7 (25.9)	17 (48.6)	14 (31.8)	12 (27.3)
	Indeterminate	0	2 (5.7)	0	0
Indeterminate	Clinical Success	18 (43.9)	13 (39.4)	1 (20.0)	2 (14.3)
	Clinical failure	6 (14.6)	7 (21.2)	1 (20.0)	2 (14.3)
	Indeterminate	16 (39.0)	13 (39.4)	3 (60.0)	10 (71.4)

*Does not include 18 subjects from 3 sites with GCP violations

The clinical efficacy reviewer did note that though many subgroups appeared to perform similarly in both arms, there were some subgroups that appeared to perform somewhat poorly in the tedizolid phosphate arm relative to the comparator or relative to the tedizolid phosphate population as a whole. The following table highlights some of these subgroups from study 112.

Table 11: Subgroup Analysis of Primary Endpoint, ITT, Study 112

	Tedizolid Phosphate N=332			Totals	Linezolid N=335			Totals
	R	N	I		R	N	I	
Overall Response	264 (79.5%)	27 (8.1%)	41 (12.3%)	332	266 (79.4%)	35 (10.4%)	34 (10.1%)	335
Age								
≥65 years old	24 (82.8%)	4 (13.8%)	1 (3.4%)	29	24 (92.3%)	1 (3.8%)	1 (3.8%)	26
Race								
African American	27 (69.2%)	2 (5.1%)	10 (25.6%)	39	31 (81.6%)	4 (10.5%)	3 (7.9%)	38
Medical History								
Diabetes Mellitus	21 (80.7%)	3 (11.5%)	2 (7.7%)	26	24 (92.3%)	1 (3.8%)	1 (3.8%)	26
Lesion Size								
≥ 1000 cm ²	15 (71.4%)	3 (14.3%)	3 (14.3%)	21	13 (92.9%)	1 (7.1%)	0	14
Region								
Latin America	6 (66.7%)	1 (11.1%)	2 (22.2%)	9	9 (75.0%)	2 (16.7%)	1 (8.3%)	12
Infection Type								
Abscess	80 (80.0%)	2 (2.0%)	18 (18.0%)	100	84 (85.7%)	1 (1.0%)	13 (13.3%)	98

R= Responder, N= Nonresponder, I= Indeterminate; Percentages are percentages of row totals

There is concern from these analyses that perhaps some vulnerable subgroups do not fare as well with the proposed 200mg dose and 6 day tedizolid phosphate regimen. However, as is clear, these subgroups were generally small and thus analyses are difficult to interpret. Also, many of these disparities could not necessarily be replicated at different time points or between studies (though some between arm disparities did remain at different time points, as in the case of diabetics in study 112 at the 48-72 hr. and EOT time point). Interestingly, if one considers the study 113 time point to be more stringent, it was notable that none of the between arm subgroup disparities noted above at 48-72 hrs. in study 112 were seen at the same time point in 113. Of course, though subgroups were chosen for analysis generally as part of standard demographic analysis or to analyze response in subjects with potentially higher disease severity, the odds of finding disparities certainly increases as more subgroup analyses are performed. Also, for within tedizolid phosphate arm comparisons, it is not necessarily surprising that some populations (patients with very large lesions sizes at baseline for example) would do poorly relative to the overall population. However, the clinical reviewer felt that despite these caveats, potentially poor activity in certain populations, particularly vulnerable ones, could not be ruled out.

Two issues of interest that could have impacted efficacy results were noted in the process of the review. First, it was noted that significant proportions of study subjects had an I&D during the course of

the study. However, when primary endpoint responder rates were compared between subjects who did and did not have an I&D, between arm comparisons did not appear to show much difference between the two arms. Within the tedizolid arm, subjects with an I&D did somewhat better on the primary endpoint compared to those who did not have these procedures in study 113 (9% difference in rates of response) but this disparity was not noted in study 112. Secondly, it was noted that there were several adverse events coded under the preferred terms abscess and cellulitis. Upon further investigation, it was noted that such adverse events could be the result of several scenarios, including the new occurrence of a secondary lesion in an area different from the primary lesion during the study, new occurrence of a secondary lesion in an area close to the primary lesion, secondary lesions at baseline that worsened, etc. In some cases these “adverse events” required treatment while in others they did not. After internal discussions, it was decided that a sensitivity analysis should be conducted where all such cases in both arms were counted as a failure according to the time period when the event occurred. For example, if such an event occurred prior to the 48-72 hr. visit, the subject would be counted as a failure from the 48-72 hr. visit (primary analysis) onwards. Similarly, if such a case occurred between the 48-72 hr. visit and EOT visit, then that subject would be counted as a failure from the EOT visit onwards. An information request was sent to the sponsor to conduct these analyses. There were 67 patients (37 in study 112 and 30 in study 113) with an adverse event of abscess or cellulitis from first dose through the PTE Visit. There were an additional 22 patients (13 in study 112 and 9 in study 113) with an adverse event of abscess or cellulitis from the PTE to the LFU Visit. The results of the sensitivity analyses are noted below for study 112 (which had “worse” results than study 113).

Table 12: Sensitivity Analyses: Abscess and Cellulitis Adverse Events Counted as Failures, ITT, Study 112

	Tedizolid Phosphate N=332 Responders/Success	Linezolid N=335 Responders/Success	Point estimate for difference	Original estimate
48-72 hr. analysis; using $\geq 20\%$ reduction criterion; no fever*	256 (77.1%)	253 (75.5%)	1.6%	1.9%
Sustained response at EOT; failures not carried forward; pain component included**	256 (77.1%)	266 (79.4%)	-2.3%	-0.2%
Investigator Assessment at PTE	264 (79.5%)	279 (83.3%)	-3.8%	-0.5%

*note that the sponsor conducted the analysis for this study using the primary endpoint for study 113

**note that the sponsor conducted this analysis with a modified version of the original secondary endpoint (failures were carried forward in original version)

As can be seen, though there were some slight changes in the point estimates of differences in response between the two arms (primarily at the later time points), the changes were relatively modest. Also, it is worth noting that the number of people to be reclassified was fairly evenly matched between both arms in Study 113 and only somewhat more prevalent in the tedizolid phosphate arm in study 112.

Finally, in terms of activity against relevant pathogens, though tedizolid phosphate appeared to have comparable activity to linezolid versus both MRSA and MSSA, its activity against other pathogens was difficult to assess given their relatively small study representation. In particular, the clinical efficacy

reviewer noted that it would be difficult to include pathogens such as *Staphylococcus haemolyticus* and *Staphylococcus lugdunensis* in labeling as an “indicated” pathogen given their very small sample size in the study (no more than 5 subjects total for both of these pathogens in both studies combined).

8. Safety

The primary safety review was conducted by Dr. Sheral Patel; the team leader was Dr. Shrimant Mishra. The primary reviewer found the application to be approvable. Her review focused primarily on data arising from the phase 2 and phase 3 trials with phase 1 data reviewed if indicated from a safety perspective.

The safety database was comprised of almost 1500 subjects with more than two thirds of subjects coming from phase 2 and 3 trials. Data from the two phase 2 trials, study 104 and study 126, and the two phase 3 trials, study 112 and study 113, were pooled into two groups for phase 2 and 3 analyses, respectively. In the phase 2 studies, patients received ≥ 200 mg tedizolid phosphate as either a disodium salt capsule (study 104) or as a free acid tablet (study 126) once daily for 5 to 7 days. In the phase 3 trials, patients received tedizolid phosphate 200 mg once daily for 6 days or linezolid 600 mg twice daily for 10 days. A tabular overview of the studies and clinical trials used to evaluate safety follows (taken from Dr. Patel’s review).

Table 13: Overview of studies and data pools used in the Safety Review

Phase	Study ID	n		Description
		Tedizolid phosphate	Linezolid	
1	15 studies	438	-	Healthy, adolescent, elderly, renally, and hepatically impaired subjects Multiple dose levels and durations
2	TR701-104	388	-	Adults with cSSSI, 200, 300, or 400 mg oral tedizolid phosphate for 5 to 7 days
	TR701-126			Adults with major cutaneous abscess or cellulitis/erysipelas, 200 mg oral tedizolid phosphate for 6 days
3	TR701-112	662	662	Adults with ABSSSI, 200 mg oral tedizolid phosphate for 6 days or 1200 mg linezolid for 10 days
	TR701-113			Adults and adolescents with ABSSSI, IV with optional oral switch 200 mg tedizolid phosphate for 6 days or 1200 mg linezolid for 10 days

The demographic data and baseline characteristics for patients enrolled in the Phase 2 studies included mean age 38.0 years, 64.7% male, 75.8% White, 26.3% Hispanic or Latino, and 2.3% ≥65 years of age. In the Phase 2 studies, 29.4% of the patients were obese (BMI ≥30 kg/m²), 34.3% of the patients had cellulitis/erysipelas and 62.9% had a major cutaneous abscess in the Phase 2 studies. Similar to the Phase 3 studies, IV drug use was reported in 30.2% of patients; 28.1% of patients had hepatic disease with 0.8% having hepatic impairment. The incidence of moderate to severe renal dysfunction (1.0%) and diabetes (7.7%) was low in the Phase 2 studies. The demographics of the phase 3 population resembled that already described in the efficacy section.

In the Phase 2 studies, the median number of doses of tedizolid phosphate administered was 6 (range 1,7). Fifty nine percent of the patients in the Phase 2 trials received 5-6 doses of tedizolid phosphate. In the Phase 3 trials, the median number of doses of active drug was 6 for tedizolid phosphate and 20 for linezolid. In the tedizolid phosphate arm, 93.5% of the patients received 5-6 doses while in the linezolid arm, 89.1% of the patients received 17-20 doses. Thus, exposure to the proposed dose and duration of tedizolid phosphate in these trials was quite good.

There were 3 deaths in the drug development program, all in the phase 3 trials; two occurred in the tedizolid phosphate arm. In one case, death occurred on Day 56 and in another case (84 year old subject with an MI 4 days after finishing the tedizolid phosphate course), there was potential confounding medical history that could have explained the event (coronary artery disease, COPD).

In the phase 3 trials there was a relatively low and comparable rate of SAEs in both arms (12 subjects [1.8%] in the tedizolid phosphate arm and 13 subjects [2.0%] in the linezolid arm) with SAEs. Infections and infestations was the most commonly reported SOC with an SAE (6 patients [0.9%] with tedizolid phosphate and 4 [0.6%] with linezolid). Notable SAEs that occurred in the tedizolid phosphate arm from the phase 2 and 3 trials include VIIth nerve paralysis and hypertension, however neither of these events were considered to be related to study drug. There was a between arm imbalance in such events occurring subjects with moderate to severe renal impairment and elderly subjects, but due to relatively small subgroup sizes and biases potentially present in such analyses, this data is difficult to interpret.

Discontinuation of study drug was low and generally comparable, occurring in 51 (7.7%) of tedizolid phosphate subjects and 61 (9.2%) of linezolid subjects in phase 3 trials. Discontinuation of study drug due to treatment emergent adverse events (TEAE) occurred in 3 (0.5%) patients in the tedizolid phosphate arm and 6 (0.9%) patients in the linezolid arm.

In the Phase 2 and Phase 3 trials, the most common treatment emergent adverse events occurring at ≥2% incidence for both tedizolid phosphate and linezolid, were diarrhea, nausea, vomiting, abscess, cellulitis, dizziness and headache. Though events in the gastrointestinal SOC class were the most frequent events in both arms (phase 3 gastrointestinal SOC events - tedizolid phosphate 106 subjects [16.0%] versus linezolid 152 subjects [23.0%], respectively), overall such events were numerically lower in the tedizolid phosphate arm. This included diarrhea (3.9% vs 5.3%, respectively), nausea (8.2% vs 12.2%, respectively), and vomiting (2.9% vs 5.6%, respectively).

In terms of general safety concerns, no signs of hepatotoxicity and renal toxicity were noted in the study population. Potentially clinically significant changes in transaminases, bilirubin and alkaline phosphatase were similar and low for tedizolid phosphate and linezolid in the Phase 3 trials. Similarly, such changes in blood urea nitrogen and creatinine were also low and comparable for both arms. Importantly, a thorough QT study was negative, and this was supported by a review of ECGs obtained from the phase 2 and 3 trials.

A primary focus of the safety review was to evaluate class (linezolid) specific safety concerns, particularly myelosuppression, peripheral and optic neuropathy, and drug drug interactions. A discussion of those findings follows:

Peripheral and ophthalmic neuropathy: A 9-month placebo-controlled rat neurotoxicology study suggested no evidence of functional or histopathologic optic or peripheral neuropathic lesions. This is in contrast to the current linezolid labeling which describes sciatic nerve damage in a 6 month rat study. A Phase 1 (study 110), open-label, single arm ophthalmology and neurology safety study of oral 200 mg tedizolid phosphate once daily for 10 days suggested no clinically meaningful changes occur in healthy adults during the course of treatment. In another small (40 subjects total, 8 in each arm) Phase 1 (study 101) randomized, placebo or active controlled double blind study where subjects received either tedizolid phosphate capsules qd at 200, 300, or 400 mg doses, linezolid 600mg bid, or placebo for up to 21 days, subjects receiving both tedizolid phosphate and linezolid had no signs of optic or peripheral neuropathy (by examination) during the study. Abnormal neurologic examinations and reported optic and peripheral neuropathy events were low and comparable for both arms in the phase 3 trials. An event of visual blurring, which can occur prior to 28 days with linezolid, was seen with tedizolid phosphate. However, because peripheral and optic neuropathy events typically occur with linezolid after a treatment duration of 28 days, the primary safety reviewer concluded that there was inadequate clinical information to truly assess the risk for these types of events with tedizolid phosphate. The only assumption that could be drawn was that the risk was similar to linezolid for the proposed dose and duration of 200mg for 6 days.

Myelosuppression: Nonclinical studies showed that tedizolid phosphate was immunotoxic and had bone marrow suppressive potential in animals at high doses. In a small (40 subjects, 8 in each arm) phase 1 (study 101) randomized, placebo or active controlled double blind study where subjects received either tedizolid phosphate capsules qd at 200, 300, or 400 mg doses, linezolid 600mg bid, or placebo for 21 days, laboratory results suggested that the risk of myelosuppression was comparable to placebo when tedizolid phosphate was dosed at 200 mg for 6 days. However, there was a decreasing trend in platelets, white blood cell counts, neutrophils and red blood cell counts at higher tedizolid phosphate doses and longer durations of treatment, though the degree of such decreases were generally less in the 200mg arm than in the linezolid or 400mg arm. In addition, the Sponsor collected data on hematology parameters during the drug development program including the Phase 2 and Phase 3 trials. Potentially clinically significant changes in platelets, white blood cell counts, neutrophils, and red blood cell counts were similar for tedizolid phosphate and linezolid in the Phase 3 trials. Linezolid associated myelosuppression generally occurs after 14 days of treatment, thus, the phase 3 studies are not adequate in realistically assessing this risk for tedizolid phosphate. However, for the proposed dose and duration, the risk seems to be similar for both arms. For potentially longer durations or higher doses of tedizolid phosphate treatment, the risk is basically unknown though the phase 1 study discussed above suggests decreased but not negligible risk of myelosuppression with the 200mg dose relative to linezolid.

MAO-related drug interactions: Nonclinical and Phase 1 studies in healthy individuals suggest that potential MAO related drug-drug interactions with tedizolid phosphate may be less than that observed with linezolid. In nonclinical studies, a tyramine challenge in rats had no significant effect on mean arterial pressure. Results from a Phase 1 study, conducted to evaluate whether 200mg tedizolid phosphate potentiates sensitivity to tyramine suggested an increased level of potentiation relative to placebo but when making crude comparisons with similar linezolid studies noted in labeling, the risk of potentiation appears to be less than with linezolid; the clinical relevance of the observed tedizolid phosphate findings in this study are unknown. In a second phase 1 study evaluating MAO-mediated pressor response to pseudoephedrine HCl in combination with placebo or 200mg tedizolid phosphate,

results did not appear to differ between the two arms. Also the pressor response itself seemed lower than for a similar study discussed in the linezolid labeling. MAO-related drug interactions could not be assessed in Phase 2 and Phase 3 trials due to study design and patient exclusion criteria. Overall, preclinical and phase 1 studies suggest that the risk of such interactions might be less than with linezolid but it is unclear if it is negligible or generalizable.

Serotonergic syndrome: Data from a study examining serotonergic brain activity in a murine behavioral model suggest no increase in head twitch rates at tedizolid phosphate exposures equivalent to 30 times the human therapeutic dose. In the Phase 2 and Phase 3 trials, patients taking concomitant serotonergic agents were excluded. In the few individuals taking concomitant 5HT₃ antagonists in the Phase 3 trials, the incidence of treatment emergent adverse events were similar for tedizolid phosphate and linezolid, and were not characteristic of serotonin syndrome. It is unclear whether the risk for this adverse event with tedizolid phosphate differs from that of linezolid

Lactic acidosis: A phase 1 study suggested that 200 mg tedizolid phosphate may not be associated with lactic acidosis up to 21 days exposure though it should be noted that it did not appear that plasma lactate levels increased with linezolid either in this study. In the Phase 2 and 3 trials, lactic acid levels were not reported and no patients were identified with substantially abnormal postbaseline bicarbonate levels. In addition, there were no patients with a treatment emergent adverse event of lactic acidosis or serum bicarbonate decreased. It is unknown whether the risk for this adverse event differs between tedizolid phosphate and linezolid.

Convulsions: There have been reports of convulsions in patients treated with linezolid. In the Phase 2 and 3 trials, no treatment emergent adverse events with the dictionary derived term of 'convulsion' or 'seizure' were identified in patients receiving tedizolid phosphate or linezolid. It is unknown whether the risk for this adverse event differs between tedizolid phosphate and linezolid

Hypoglycemia: Symptomatic hypoglycemia has been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with linezolid. In the Phase 2 and 3 trials, no treatment emergent adverse events with the dictionary derived term of 'hypoglycemia' or 'blood sugar decreased' were identified in patients receiving tedizolid phosphate or the comparator. TEAEs in the subset of patients with diabetes were similar in the tedizolid phosphate and linezolid arms in the Phase 3 trials. It is unknown whether the risk for this adverse event differs between tedizolid phosphate and linezolid.

Patient Subpopulations: When looking at the adverse event profile in phase 3 subjects with moderate to severe renal failure, 11 of 20 (55.0%) patients in the tedizolid phosphate arm experienced TEAEs, compared with 8 of 29 patients (27.6%) in the linezolid arm. In addition, there were 2 and 5 patients with severe and serious TEAEs, respectively, in the tedizolid phosphate arm versus none in the linezolid in the arm. Similarly in subjects ≥ 65 years old, there were 6 of 72 (8.3%) subjects and 1 of 59 (1.7%) subjects who had serious TEAEs in the tedizolid phosphate and linezolid arms, respectively (similar findings were noted in subjects ≥ 75 years old). Given the small size of these subgroups, it is difficult to draw any definitive conclusions. In subjects with hepatic impairment there is no increase in the adverse event profile relative to linezolid, however these subgroups are too small to make any real comparisons.

There was no recommendation made for post-market risk evaluation and mitigation strategies.

9. Pediatrics

Currently the applicant is deferring pediatric studies until after potential approval of the drug in adults. Though a PK study has already been conducted in adolescents, further PK studies in subjects aged 0- < 12 years and safety and efficacy studies from age 0 to 18 years are planned post-approval. Of note, in subjects aged 0- 3months, the indication studied will be hospital acquired late onset sepsis rather than ABSSSI. The plan has been evaluated by PERC and was generally found acceptable though PERC recommended shortening the timelines for the initiation of some of the studies. At the time of this review, final comments about the pediatric study plan are being drafted to send to the applicant.

10. Advisory Committee Meeting

The Anti-Infective Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on March 31, 2014. A verbatim transcript is posted on the FDA website at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm385739.htm>

The members and temporary voting members were provided the background materials from the FDA and Cubist Pharmaceuticals, which had acquired Trius Pharmaceuticals prior to the meeting. There were approximately 175 people in attendance and six Open Public Hearing speakers.

The following questions were posed to the committee for deliberation.

1. *Has the applicant provided substantial evidence of the safety and effectiveness of tedizolid phosphate for the treatment of acute bacterial skin and skin structure infections caused by susceptible isolates of the designated microorganisms?*
 - a. *If yes, please provide any recommendations concerning labeling.*
 - b. *If no, what additional studies/analyses are needed?*

All committee members voted “Yes”, indicating that the applicant provided substantial evidence of the safety and effectiveness of tedizolid phosphate for the treatment of acute bacterial skin and skin structure infections caused by susceptible isolates of the designated microorganisms. Emerging themes in the discussion by the committee members included the following:

- 1.) Lack of diverse patient population, particularly in the pivotal trials. Further study is required in patient subgroups and clarification should be provided in the label.
- 2.) Reluctance to approve tedizolid phosphate for use in adolescent patients based on the data at hand. Clarification should be provided in the label.
- 3.) Pediatric studies should be conducted.

- 4.) Safety issues with tedizolid phosphate for treatment course beyond 6 days require further study. Clarification should be provided in the label.
- 5.) Reluctance to approve tedizolid phosphate for use in neutropenic patients based on the data at hand. Clarification should be provided in the label.
- 6.) Consider a warning to address the potential for cross-resistance of tedizolid phosphate with linezolid.
- 7.) Ensure that there is enough microbiologic data to support indicated organisms in the label.
- 8.) Further data is needed for drug-drug interactions.
- 9.) Results of the MITT analyses should be included in label.
- 10.) Differences for dosing, safety and efficacy for obese patient, if any, should be clarified in the label.

11. Other Relevant Regulatory Issues

Four study sites were chosen for inspection, primarily due to study enrollment numbers (OSI's site inspection tool was utilized in this process). Of the four sites, 3 were domestic and one was an international site in Russia. Due to factors outside of Agency control (namely a tense current foreign policy relationship with Russia), access to the Russian site has been prohibited; it is unlikely to be inspected before the PDUFA goal date if at all. Inspection results of the other 3 sites as well as a sponsor site were generally positive; no major findings were discovered that could potentially affect the phase 3 safety and efficacy results. It should be noted that the audit of the sponsor site included review of the oversight and communication with the Russian site and was found to be acceptable.

Upon its own internal review, the sponsor noted that 3 sites, sites 120, 121, and 122 in study 112, did not appear to adhere to accepted cGCP practices. In particular, it was noted that there were deficiencies in source documents (including multiple and hard to interpret corrections, lack of source documentation, etc.) that did not allow for proper corroboration of eCRF data. Moreover, these sites appeared to have poor management and operating practices including inadequate training, poor maintenance of documentation, poor storage of documents, and poorly understood delegation of authority. Also, in some instances, infection types were reclassified without proper documentation as to the reason for this. Though the sponsor concluded that subjects at these sites were in general properly screened and randomized, received proper treatment, and followed the protocol, due to issues with source documentation, it was recommended to exclude these subjects from efficacy analyses. These sites only enrolled 18 subjects, and the statistical reviewer performed most study 112 analyses using the ITT population exclusive of these subjects; these analyses did not appear to change the overall study conclusions. The primary efficacy reviewer conducted analyses using the original ITT population. As noted above, DSI has not inspected these sites yet (but will do so for another drug product) and has recommended sensitivity analyses excluding these subjects. All 18 patients from the 3 sites with GCP violations were included in the safety analyses. None of these patients had serious adverse events. No significant financial disclosure issues were noted.

The applicant conducted a Phase 1 study (study 110) in volunteers where detailed assessments of ophthalmic and peripheral neurologic function were conducted. No associated risk of optic neuropathy was seen with administration of 200 mg once daily tedizolid phosphate for 10 days after 4-6 weeks of follow-up after the screening examination. In addition, the FDA Division of Transplant and

Ophthalmology Products was consulted during the IND phase of drug development to comment on study 110. They concluded that there were no clinically significant treatment-related effects on visual acuity, slit lamp examination, optic nerve, color vision, or visual field identified in this clinical trial.

12. Labeling

DRISK evaluated the application and no REMS was recommended. DDMAC and DMEPA also evaluated the label and their labeling suggestions have been incorporated into the final proposed PI sent to the applicant for review. The trade name (SIVEXTRO) was evaluated by DMEPA and found to be acceptable in December 2013.

Important labeling proposals forwarded on to the applicant include:

1. Placing a Warning and Limitation of Use regarding use in neutropenic patients
2.  (b) (4)
3. Revising section 6 (Adverse Reactions) to be similar to the dalbavancin label
4. Adding language in section 6.1 stating that no data beyond 6 days of usage is available to evaluate peripheral and optic neuropathy risk
5. Adding language in section 6.1 describing a possible dose and duration effect of tedizolid phosphate on myelosuppression in phase 1 studies
6. Adding adverse reactions of interest in section 6.1 such as paresthesias and visual blurring
7. Not granting use below 18 years of age in section 8.5
8. Highlighting insufficient data to make any claims regarding safety and efficacy in the elderly in section 8.5
9. Describing the phase 1 pseudoephedrine and tyramine studies in greater detail in section 12.3
10.  (b) (4) clarifying salient microbiological issues in section 12.4
11. Describing nonclinical study results related to bone marrow suppression and immunotoxicity in section 13.2
12. Describing study 112 and 113 individually in section 14.1 with a focus on the primary endpoint and the investigator assessment at PTE

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action for this application is that it should be approved for the indication of ABSSSI for the studied dose and duration (200mg of tedizolid phosphate for 6 days). Noninferiority was demonstrated in two randomized, blinded, active controlled phase 3 trials, and there were no major safety concerns to preclude approval. The approval should be for both the 200mg intravenous and oral formulation as high bioavailability of the oral formulation was demonstrated.

- **Risk Benefit Assessment**

There is an overall positive risk benefit calculus for this application. The study drug appears to be efficacious in the claimed indication of ABSSSI with a shortened regimen duration relative to the comparator. It also appears to be relatively safe for the dose and duration studied, and there were no major manufacturing concerns. Because of its high bioavailability, simple pharmacokinetic profile (with no real dose adjustment for the subpopulations studied), and once a day dosing regimen, it should be able to be used with ease in many populations and clinical settings. Interestingly, the drug may possess some activity against a small portion of linezolid resistant strains which could prove to be important in the future (depending on how resistance patterns evolve over time). Thus, as a whole, tedizolid phosphate offers another useful alternative for treating gram positive ABSSSI's, including those infections caused MRSA.

However, it is also clear that despite the consensus among the various disciplines for approval, there remain several unknowns associated with the drug. With regards to efficacy, there remains concern that certain subgroups, particularly certain vulnerable populations, may not fare as well relative to comparators or the overall population at the proposed dose and duration. Whether such concerns are misplaced given the dubious usefulness of subgroup analyses or whether they represent a situation where the proposed dose and duration is insufficient is unknown and will likely be further sorted out over time in the actual health care setting. More concerning seems to be the drug's implicit reliance on neutrophils for its activity. Such a phenomenon makes it unclear whether the drug would perform well in settings of neutropenia, poor neutrophil function, or in other settings where immune function is compromised. Indeed, it's unclear how the demographics of the phase 3 studies (with its large representation of IV drug users) can be generalized to the ABSSSI patient population at large, and it remains to be seen whether over time the drug's use becomes limited to relatively young, healthy subjects with moderate infections.

From a safety perspective, it still remains unclear whether tedizolid phosphate represents a safer oxazolidinone relative to the typical toxicities associated with linezolid. At the proposed tedizolid phosphate dose and duration (200mg for 6 days), class specific toxicities seemed equally low in both arms, however what that portends in a larger population or for longer, potentially off label use is unclear. Nonclinical studies seemed to suggest that at least some class specific toxicities (myelosuppression, mitochondrial effects) were present with tedizolid phosphate albeit at exposure levels higher than what was expected in humans. Phase 1 studies

either seemed to suggest that certain class specific toxicities (as in the case of myelosuppression) might occur with higher doses and longer durations or were simply conducted for too short a time to draw any definitive conclusions (as in the case of peripheral and optic neuropathy). It is entirely possible, that in some instances, the safety profile may be somewhere in between that of placebo and linezolid (as is possibly the case with MAOI inhibition), and it will require more time and investigation to better understand the clinical relevance of such findings. An important point to emphasize is that though the safety of tedizolid phosphate is being discussed in its relation to class specific toxicities, currently there is only one approved oxazolidinone (linezolid) and thus there is no clear background understanding of the full breadth of class toxicities. Our knowledge of class specific toxicities is almost certain to evolve with the approval and use of tedizolid phosphate. Lastly, due to a paucity of information, use in adolescents cannot be recommended at this time.

Thus, as is the case with the approval of many drugs, there are some important assurances about the safety and efficacy of tedizolid phosphate in the treatment of ABSSSI, and these assurances tilt the overall risk benefit calculus in favor of approval. However, there are still several unanswered questions which will likely only be answered as we gain more clinical experience with the drug.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

There is nothing in the overall review of the application to suggest that a REMS would be valuable. Of course, if postmarketing experience uncovers important safety findings then the value of a REMS or other Agency safety measure would have to be revisited

- **Recommendation for other Postmarketing Requirements and Commitments**

Only two PMR's are currently being requested. The first is the usual division request for a multiyear surveillance study of relevant clinical isolates to assess patterns of tedizolid resistance. The second involves the requirement that the sponsor complete its proposed pediatric studies as required under PREA. Timelines for these requirements are currently being devised.

(b) (4)

- **Recommended Comments to Applicant**

No comments to be conveyed outside of labeling.

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/s/

SHRIMANT MISHRA
06/09/2014