Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Options Review

Date:	May 5, 2014
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Drug Name(s):	Tedizolid phosphate
Therapeutic Class:	oxazolidinone
Dosage and Route:	Oral: 200 mg once daily for 6 days Intravenous: 200 mg every once daily for 6 days
Application Type/Number:	NDA 205435 (oral) and 205436 (intravenous)
Applicant/sponsor:	Trius Therapeutics Inc.
OSE RCM #:	2013-2707, 2013-2708

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity tedizolid phosphate. The Agency received the new drug application (NDA) from Trius Therapeutics Inc for tedizolid on October 21, 2013. The proposed indication is "for the treatment of acute bacterial skin and skin structure infections (ABSSSI) [1] caused by susceptible isolates of the following gram-positive micro-organisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible[MSSA] isolates, and cases with concurrent bacteremia), *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group (including *Streptococcus anginosus*, *Streptococcus intermedius* and *Streptococcus constellatus*), and *Enterococcus faecalis*."

Trius did not propose a REMS or submit a risk management plan.

1.1 BACKGROUND

According to the Centers for Disease Control and Prevention, studies show that about one in three people carry staphylococcus in their nose, usually without any illness. Two in 100 people carry MRSA. Most staphylococcus infections, including MRSA present as a bump or infected area on the skin and "recent data suggest that MRSA as a cause of skin infection in the general community remains a high probability."[2]

The Infectious Disease Society of America (IDSA) last published practice guidelines for the "diagnosis and management of skin and soft-tissue infections" in 2005. This guideline lists the following options for MRSA skin and soft-tissue infections:

- Vancomycin
- Linezolid
- Clindamycin
- Daptomycin
- Doxycycline[3], minocycline[4]
- Trimethoprim sulfamethoxazole[3]

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[1] Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185.pdf. This Guidance explains, among other things, the switch from complicated skin and skin structure infections to the acute skin and skin structure infections.

[2] http://www.cdc.gov/mrsa/ - accessed April 24, 2014.

[3] Not approved for treatment of skin or skin structure infections.

[4] The Minocycline labeling states, "Minocycline is indicated for skin and skin structure infections caused by staphylococcus aureus (note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection)."

Since 2005, the following drugs were approved for the treatment of skin and skin structure infections including infections caused by MRSA:

- Tigecycline – approved 2005; indicated for complicated skin and skin structure infections
- Telavancin – approved 2009; indicated for complicated skin and skin structure infections
- Ceftaroline fosamil – approved 2010; indicated for acute skin and skin structure infections

In January 2011, IDSA published their first practice guideline for the treatment of MRSA infections in adults and children.

- For **outpatients** with skin and soft tissue infections in the era of community acquired MRSA, the recommended oral empirical antibiotic treatment options are: clindamycin, trimethoprim sulfamethoxazole, doxycycline/minocycline, and linezolid.
- For **hospitalized patients** with skin and soft tissue infections in the era of community acquired MRSA, the recommended empirical antibiotic treatment options are: vancomycin (IV), linezolid (IV or oral), daptomycin (IV), telavancin (IV), and clindamycin (IV or oral).

Tedizolid phosphate is a oxazolidinone prodrug that is converted in vivo by phophastases to the microbiologically active antibiotic tedizolid; interfering with protein translation by binding to the 50S subunit of the bacterial ribosome. Tedizolid is administered as 200 mg IV or oral once daily for 6 days. Currently linezolid (Zyvox) is the only approved oxazolidinone-class antibiotic approved. Linezolid dosing offers IV to oral switch option.

2 MATERIALS REVIEWED

- October 21, 2013 NDA 205435 (oral) and 205436 (intravenous).
- March 31, 2014. FDA Briefing Document and Slide Presentation for Anti-Infective Drugs Advisory Committee Meeting. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm385739.htm.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

Sections 3.1 and 3.2 of this review include excerpts from the FDA's Anti-Infective Advisory Committee Meeting Briefing Document for the March 31, 2014 meeting.

The Phase 3 development program for tedizolid consisted of two trials, Study TR701-112 and Study TR701- 113.

- TR701-112 was a randomized, active controlled, double-blind, double dummy, multicenter noninferiority (NI) trial comparing 6 days of oral tedizolid 200 mg daily with 10 days of oral linezolid 600 mg twice daily for the treatment of ABSSSI.

Subjects were enrolled in 82 sites worldwide. Subjects were randomized 1:1 to either oral tedizolid 200 mg daily for 6 days or oral linezolid 600 mg twice daily for 10 days. The primary outcome measure was early clinical response at the 48-72 hour visit. The primary analysis population was the intent-to-treat (ITT) population.

There were 667 subjects randomized and included in the ITT population, 332 subjects in the tedizolid arm and 335 in the linezolid arm. Over 90% of subjects in both arms completed the study. For the primary efficacy endpoint, in the ITT*[5] population, 79.3% of patients in the tedizolid phosphate group and 79.1% of patients in the linezolid group were responders.

- TR701-113 was a randomized, double blind, double dummy, active controlled, multicenter, NI trial that compared a 6 day regimen of daily 200 mg IV to oral tedizolid with a 10 day regimen of twice daily 600 mg IV to oral linezolid in the treatment of ABSSSI. The primary outcome measure was at 48-72 hours after the first infusion of study drug, the subject was determined to be a responder or nonresponder based on specified criteria.

  There were 666 patients randomized and included in the ITT population, 332 in the tedizolid arm and 334 in the linezolid arm. Over 90% of subjects in both arms completed the study.

  The following table from the FDA Briefing Document provides the results of studies TR 701-112 and TR 701-113, using two efficacy endpoint definitions: (1) cessation of spread defined as no increase in baseline lesion size and no fever criteria and (2) ≥20% decrease from baseline at 48-72 hour visit in lesion area, no fever criteria (also includes no use of antibacterial drugs and alive).

Table: Efficacy definitions of ECE at 48-72 hours without fever component

Efficacy Definitions	**TR 701-112 (ITT*)**		**TR 701-113 (ITT)**	
	Tedizolid phosphate	**Linezolid**	**Tedizolid phosphate**	**Linezolid**
	N = 323	**N = 326**	**(N = 332)**	**(N = 334)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
48-72 Hour Response (Cessation of spread as no increase from baseline in area, no fever component)				
Responder	280 (86.7)	277 (85.0)	310 (93.4)	302 (90.4)
Difference	1.7 (-3.7, 7.1)[1]		3.0 (-1.2, 7.2)[1]	
Nonresponder or indeterminate	43 (13.3)	49 (15.0)	22 (6.6)	32 (9.6)
Nonresponder	20 (6.2)	25 (7.7)	17 (5.1)	18 (5.4)
Indeterminate	23 (7.1)	24 (7.4)	5 (1.5)	14 (4.2)
≥20% decrease from baseline at 48-72 hour visit in lesion area, no fever criteria				

[5] In Study TR 701-112, the applicant identified issues at three sites that raised concerns that the source data did not fully meet Good Clinical Practices standards. These sites enrolled 18 patients, equally distributed between the two treatment arms, The change in efficacy was negligible when the 18 patients were removed from the ITT analysis.

Responder	252 (78.0)	246 (75.5)	283 (85.2)	276 (82.6)
Difference	2.6 (-4.0, 9.1)[1]		2.6 (-3.0, 8.2)[1]	
Nonresponder or indeterminate	71 (47.0)	80 (24.5)	49 (14.8)	58 (17.4)
Nonresponder	48 (14.9)	56 (17.2)	44 (13.3)	44 (13.2)
Indeterminate	23 (7.1)	24 (7.4)	5 (1.5)	14 (4.2)
[1]95% unadjusted CI for the treatment difference				

3.2 SAFETY CONCERNS

Currently linezolid is the only approved oxazolidinone-class antibiotic approved. The approved labeling for linezolid lists the following Warnings:

- Myelosuppressiopn
- Peripheral and optic neuropathy
- Serotonin syndrome
- Mortality imbalance in an investigational study in patients with catheter-related bloodstream infections, including those with catheter-site infections
- *Clostridium difficile* associated diarrhea
- Potential interactions producing elevation of blood pressure
- Lactic acidosis
- Convulsions
- Hypoglycemia
- Development of drug resistant bacteria

According to the FDA Briefing Document, the applicant's overall safety evaluation plan included studies to detect specific adverse reactions that could potentially occur with the use of tedizolid phosphate including general areas such as QT prolongation, hepatotoxicity and renal toxicity, as well as, oxazolidinone class specific concerns (outlined in the linezolid Warnings above). The following potential adverse events were discussed in the FDA Advisory Committee Briefing Document:

- Neurologic disorders: In the Phase 3 trials, there were 8 (1.2%) patients in the tedizolid phosphate arm and 5 (0.8%) in the linezolid arm who experienced at least one neurologic TEAE. These events included hypoesthesia, cranial nerve VII paralysis, parasthesia and sensory loss. Most events were mild and transient.

- Optic nerve disorders: In Phase 3 trials, there were two (0.3%) patients in the tedizolid phosphate arm and one (0.2%) in the linezolid arm with at least one optic nerve disorder TEAE. These events included visual acuity reduced and visual impairment. Both events were classified as not related to study drug.

- Myelosuppression: In Phase 3 trials, there was one patient in the tedizolid phosphate arm who had a study drug related TEAE 'white blood cell count decreased'.

- Lactic acidosis: Lactate levels were not reported in Phase 2 and Phase 3 trials.

- Convulsions: There were no patients identified with TEAE of convulsion or seizure during the Phase 2 and Phase 3 trials.

- Serotonin syndrome: The review team analyzed patients on concomitant serotonin antagonists who reported at least one TEAE. The relevant adverse events reported for patients on tedizolid included asthenopia, muscle spasms, dizziness, headache, insomnia, and flushing

The distribution of events over mild, moderate, and severe categories was similar between the tedizolid phosphate and linezolid arms.

Treatment Emergent Adverse Events (TEAE)

According to the FDA Briefing Document, the highest incidence of TEAEs was in the GI disorders (16.0% in the tedizolid phosphate group and 23.0% in the linezolid group).

- In Phase 3 trials, events occurring at ≥5% incidence included nausea, headache, and abscess in the tedizolid group and nausea, headache, diarrhea, and vomiting in the linezolid group. Nausea and vomiting were less frequent in the tedizolid phosphate group (8.2% and 2.9%, respectively) compared to the linezolid group (12.2% and 5.6%, respectively).

- In Phase 3 trials, the overall incidence of TEAEs attributed by the investigator as related to the study drug was 22.4% (148 patients) in the tedizolid phosphate group and 27.9% (185 patients) in the linezolid group.

Serious Adverse Events (SAEs)

According to the FDA Briefing Document, the incidence of SAEs occurring in patients receiving tedizolid and linezolid was similar. The majority of the SAEs reported were considered unrelated to tedizolid or linezolid.

- In Phase 3 trials, SAEs occurred in 12 patients (1.8%) in the tedizolid phosphate group and in 13 patients (2.0%) in the linezolid group. Infections and infestations were the most commonly reported system organ class (SOC) with SAEs (6 patients [0.9%] with tedizolid and 4 [0.6%] with linezolid). One event was reported in both groups (urinary tract infection in 1 patient each).

Deaths

There were three deaths reported in the drug development program, all occurring during the Phase 3 trials. None appeared related to the tedizolid or linezolid. The two patients receiving tedizolid phosphate were elderly and had multiple comorbidities. The third death occurred in a patient on linezolid who was HIV positive with a low CD4 count.

4 DISCUSSION

The Anti-Infective Advisory Committee convened on March 31, 2014 to discuss tedizolid. The Committee voted unanimously (14 to 0) that "the applicant provided substantial evidence of the safety and effectiveness of tedizolid phosphate for the treatment of ABSSSI caused by susceptible isolates of the designated microoganisms."

Based on the available safety information, DRISK does not recommend a REMS for management of the risks associated with tedizolid. The safety profile is consistent with linezolid which does not have a REMS.

5 CONCLUSION

DRISK concurs with the Division of Anti-Infective Products that, based on the available data and the potential benefits and risks of treatment, at this time a REMS is not necessary for tedizolid. If new safety information becomes available that changes benefit risk profile this recommendation can be reevaluated.

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/s/

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