

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207953Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**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) Review

Date: May 15, 2015

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Subject: Review to determine if a REMS is necessary

Drug Name(s): Yondelis (trabectedin)

Therapeutic Class: antineoplastic

Dosage and Route: 1.5 mg/m² as 24-h IV infusion every 3 weeks

Division: Division of Oncology Products – 2 (DOP-2)

Application Type/Number: NDA 207953

Applicant/sponsor: Janssen Products LP

OSE RCM #: 2014-2472
2014-2494

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1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is necessary for the new molecular entity (NME) Yondelis (trabectedin). The applicant, Janssen Products LP, submitted a New Drug Application (NDA) 207953 for trabectedin (b) (4)

Janssen Products LP submitted a risk management plan with identified risks of hypersensitivity reactions, multi-organ failure, hepatotoxicity, neutropenia, thrombocytopenia, anemia, creatine phosphokinase (CPK) elevations and/or rhabdomyolysis, respiratory disorders, emesis, and injection site reactions. Potential risks associated with trabectedin were identified in the risk management plan as pancreatitis, acute myeloid leukemia, and reproductive toxicity. Janssen's submission included a pharmacovigilance plan, which proposed to manage these events through routine pharmacovigilance and product labeling. Janssen did not submit a REMS.

1.1 BACKGROUND¹

The American Cancer Society estimates that approximately 11,930 new cases of soft tissue sarcoma will be diagnosed (6,610 cases in males and 5,320 cases in females) in the United States in 2015. Soft tissue sarcoma deaths are expected to be close to 4, 870 per year.² The most frequent histopathologic types of soft tissue sarcoma are leiomyosarcoma and liposarcoma which make up 40-50% of all cases of soft tissue sarcoma. The current treatment for soft tissue sarcoma is a combination of surgery, radiotherapy, and chemotherapy. First line treatment is doxorubicin as single agent treatment or combination with ifosfamide. Refractory treatment includes treatment with dacarbazine, ifosfamide, gemcitabine, taxanes, and pazopanib. Despite the available chemotherapy options, the prognosis for patients with soft tissue sarcoma remains very poor, with an estimated median survival of 8 to 14 months from the start of first-line doxorubicin and limited treatment options exist for 50% of patients who present with or develop advanced disease.

Trabectedin - Trabectedin is an intravenous antineoplastic agent which binds to the N2 position of guanine in the groove of deoxyribonucleic acid (DNA). This binding to DNA triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways resulting in perturbation of the cell cycle, and p53 apoptosis.¹ The proposed indication for trabectedin is (b) (4)

¹ Clinical Overview (section 2.5), trabectedin

² <http://www.cancer.org/cancer/sarcoma-adultsofttissuecancer/detailedguide/sarcoma-adult-soft-tissue-cancer-key-statistics> accessed 3/3/15

The recommended dose of trabectedin is 1.5 mg/m² body surface area (BSA) administered over 24 hours as an intravenous (IV) infusion once every 3 weeks. Trabectedin was granted marketing authorization by the European Medicines Agency in 2007 for the treatment of patients with STS who have progressed after both anthracycline and ifosfamide treatment.

1.2 REGULATORY HISTORY

The review timeline for this application is Priority. Listed below are the pertinent regulatory history milestones for this NDA:

- April 7, 1996 – IND 50286 submitted for trabectedin for STS
- November 24, 2014 –NDA application received
- March 30, 2015 – Midcycle meeting
- April 23, 2015 – Midcycle teleconference with the sponsor
- PDUFA (Action) date – July 24, 2015

2 MATERIALS REVIEWED

- Pfizer Clinical Modules (sections 2.5, 2.7.3 and 2.7.4)
- Risk Management Plan submitted December 16, 2014
- Midcycle Slides Presented on March 30, 2015
- Yondelis (trabectedin) draft label, April 17, 2015
- Draft clinical review by Drs. Amy Barone & Dow-Chung Chi (v. April 9, 2015)

3 RESULTS OF REVIEW^{4,5}

With respect to STS, 4 Phase 2 studies supported the 2007 approval of trabectedin for the indication of STS in the EU and other countries and included 3 single-arm Phase 2 studies conducted in a total of 183 subjects with advanced STS and a randomized Phase 2 study in a total of 270 patients. Data from 2 studies were submitted to this NDA. This included the pivotal Phase 3 study (ET743-SAR-3007) and the supportive Phase 2 study, (ET743-ST-201).

For the purpose of this NDA, the key clinical study is the pivotal phase 3 study.

3.1 OVERVIEW OF CLINICAL PROGRAM

At the time of this writing, FDA clinical reviewers were still completing analysis of the safety and efficacy of the studies outlined below. The summary below provides a high level overview of the studies that support this application.

Key Efficacy Findings: Please refer to the clinical review by Drs. Amy Barone and Dow-Chung Chi for the full review on efficacy and safety. The following is a summary of the key findings from substantially complete labeling for trabectedin as of **April 17, 2015**.

³ Yondelis (trabectedin) draft label, April 17, 2015

⁴ Trabectedin Summary of Clinical Efficacy Section 2.7.3

⁵ Draft clinical review by Drs. Amy Barone & Dow-Chung Chi (v. April 9, 2015)

Study ET743-SAR-3007 This was a randomized, open-label, active-controlled, parallel group, multicenter study that evaluated the safety and efficacy of trabectedin as compared with dacarbazine in adult subjects with unresectable, advanced or metastatic L-type sarcoma, who were previously treated with at least an anthracycline and ifosfamide containing regimen or an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen.

Patients enrolled in this study had a median age of 56 years in the trabectedin arm and 56 years in the dacarbazine arm. Seventy-six percent of patients were white and all patients had an ECOG PS of 0. Twenty-seven percent of 345 patients had liposarcoma and 73% had leiomyosarcoma.

Five hundred eighteen patients were randomized in this study in a 2:1 ratio with 345 to the trabectedin group and 193 to the dacarbazine group. Enrollment occurred in 4 countries (Australia, Brazil, New Zealand, and the United States of America [US]) at 85 sites (94% of patients were enrolled at US sites).

Study treatments were scheduled on Day 1 of each 21-day cycle as follows:

- Trabectedin Group (n≈380 subjects): 1.5 mg/m² as 24-h IV infusion q 3 weeks. Subjects received pretreatment with 20 mg of dexamethasone IV, or an equivalent IV corticosteroid, on Day 1 of each treatment cycle, 30 minutes before study drug.
- Dacarbazine Group (n≈190 subjects): 1 g/m² as a 20-120 minute IV infusion q 3 wk.

Patients received study treatment until progressive disease, unmanageable toxicity, or consent withdrawal.

The primary endpoint for this study was whether overall survival (OS) for the trabectedin group was superior to the dacarbazine group for patients with advanced L-type sarcoma who were previously treated (in any order) with at least an anthracycline and ifosfamide containing regimen or an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen. Median OS was 13.7 months for the trabectedin group and 13.1 months for the dacarbazine group. Secondary objectives were to evaluate disease control, as assessed by progression free survival (PFS), time to treat, overall response rate, and duration of response as well as symptom severity (i.e., patient reported outcomes) and safety in the trabectedin and dacarbazine groups. Treatment with trabectedin resulted in a 45% reduction in the risk of progressive disease or death compared with dacarbazine treatment. The median PFS was 4.2 months for patients treated with trabectedin compared to 1.5 months for patients treated with dacarbazine.

3.2 SAFETY CONCERNS^{3,6}

The safety of trabectedin (dose) is based on analysis of data from 340 patients in Study ET743-SAR-3007, 865 patients from 10 studies in the STS integrated data analysis set, and 1681 patients from 24 studies in the STS and other solid tumor analysis set (2.7.4). Of the 865 patients in the STS integrated data analysis set, 717 of these patients were on the q 3 wk; 24-h (1.5 mg/m²) dosing regimen and 944 in the STS and other solid tumor analysis set.

The data described below reflect exposure to trabectedin in the q 3 wk; 24-h dosing regimen. Patients received, on average, 4 cycles of trabectedin. The median duration of treatment for trabectedin was 12 weeks while the median duration of treatment on the dacarbazine arm was 7 weeks.

Grade 3-4 treatment emergent adverse events (TEAEs) occurred in 62.3% of subjects; 45.6% of patients had drug-related Grade 3-4 TEAEs. The most common Grade 3-4 toxicities with trabectedin were laboratory-related treatment emergent adverse events (TEAEs) such as bone marrow suppression and hepatotoxicity. Grade 3-4 TEAEs that occurred at a 10% or higher frequency in the trabectedin group were increased alanine transaminase (ALT), decreased WBC count, and increased aspartate transaminase (AST), and neutropenia while the most frequently reported TEAE in the dacarbazine arm was anemia.

Dose reductions due to an adverse reaction of any grade occurred in 35.0% of patients receiving trabectedin and 56.8% of patients requiring a cycle delay. All dose reductions were due to TEAEs. Most common drug-related TEAEs leading to a reduction in the dose of trabectedin in 3% or more of subjects included neutropenia and increases in ALT, AST and ALP; all occurred at incidences higher than reported for dacarbazine-treated subjects. The 4 most prevalent dacarbazine-related TEAEs leading to a dose reduction included decreased platelet counts, neutropenia, thrombocytopenia, and fatigue.¹ Most dose reductions in the trabectedin group occurred by the 4th cycle with only 28.2% of patients requiring only 1 cycle delay. If the following events occurred at any time between cycles: platelets were < 1000/microliters with fever/infection or <500/microliters lasting >5 days, total bilirubin and ALP liver fraction or 5' nucleotide elevation >ULN, transaminase elevation was Grade ≥ 3, or nausea or vomiting of Grade ≥ 3 despite pre-medication, trabectedin dose was to be reduced to 1.2 mg/m² in subsequent cycles. If any of the events reappeared in subsequent cycles, the trabectedin dose was to be reduced further to 1 mg/m². If further dose reductions were necessary, trabectedin was to be discontinued. If toxicities preventing retreatment persisted beyond 3 weeks, treatment was to be discontinued.

Treatment discontinuation due to TEAE occurred in 10.6% of patients receiving trabectedin and in 7.7% patients receiving dacarbazine. Overall, serious TEAEs that resulted in discontinuation of trabectedin were dyspnea, rhabdomyolysis, respiratory failure, fatigue, febrile neutropenia, pleural effusion, renal failure, and small intestinal obstruction.

⁶ Trabectedin Summary of Clinical Safety Section 2.7.4

Permanent discontinuation due to an adverse reaction due to a TEAE was 10.0% higher in trabectedin group versus 7.1% in the dacarbazine group.

Deaths: In Study ET743-SAR-3007, 126 subjects (37.1%) in the trabectedin treatment group and 60 subjects (38.7%) in the dacarbazine treatment group died during treatment or follow-up. Deaths within 30 days of last dose occurred in 6.5% of the trabectedin group and 1.9% of the dacarbazine group. Of these deaths, half of the trabectedin deaths (3.2%) and all of the dacarbazine deaths (1.9%) were due to disease progression. The remaining 11 deaths (3.2%) in the trabectedin group were due to TEAEs; of these deaths, the TEAEs leading to the death of 7 subjects (2.1%) were assessed by the investigator as drug-related. Deaths within 60 days from initiation of treatment occurred in 24 subjects (7.1%) for the trabectedin treatment group and 9 subjects (5.8%) in the dacarbazine treatment group.

These adverse events will be managed in labeling under separate subsections under Warnings and Precautions.

The applicant plans to communicate all safety events through labeling, and therefore did not submit a REMS.

4 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

PMR's and PMC's have not been finalized at the time of this writing.

5 DRISK ASSESSMENT OF RISK AND NEED FOR A REMS

DRISK has the following comments on several factors that are considered in the assessment of the need for a REMS for trabectedin.

Trabectedin is an intravenous, antineoplastic for the proposed indication (b) (4)

The most common Grade 3 or 4 TEAE of trabectedin were neutropenia and elevated hepatic transaminases. These events were commonly seen in this patient population and were handled adequately by dose reduction and cycle delay. Both events will be communicated in product labeling under Warnings & Precautions.

Current FDA-approved therapies for the treatment of advanced soft tissue sarcoma include surgery, radiotherapy, and chemotherapy. Initial chemotherapy for patients with advanced or metastatic STS typically consists of an anthracycline (mainly doxorubicin) as a single agent or in combination with ifosfamide. After treatment with front-line anthracyclines, subsequent therapy choices for the treatment of refractory disease include dacarbazine, ifosfamide, gemcitabine, the taxanes, and pazopanib. Dacarbazine is the recommended treatment option for STS by experts and guidelines after failure of anthracyclines and ifosfamide.

Myelosuppression is common amongst all of these agents. Nausea is common between dacarbazine, doxorubicin, ifosfamide and trabectedin. With pazopanib, a Boxed Warning is used to describe effects of hepatotoxicity which include increases in serum transaminases (ALT and AST) and bilirubin and death. For doxorubicin, a Boxed Warning is used to describe the effects of cardiomyopathy, secondary malignancies, extravasation and tissue necrosis, and severe myelosuppression. For ifosfamide, a Boxed Warning is used to describe the effects of myelosuppression and neuro- and urotoxicity. None of these agents required a REMS for approval.

Anticipated Patient Population: The target population will include patients with advanced soft tissue sarcoma, liposarcoma, and leiomyosarcoma subtypes who have received prior chemotherapy. Despite the availability of several medications for the treatment of advanced soft tissue sarcoma, for the 50% of patients who experience metastatic disease, the prognosis is poor, with an estimated median survival of 8 to 14 months from the start of first-line cytotoxic therapy.⁴ Trabectedin was shown to be similar to dacarbazine with regard to the OS, resulting in a 12 month median OS concurrent with dacarbazine, and the median PFS which was 4.2 months for patients treated with trabectedin compared to 1.5 months for patients treated with dacarbazine.

Anticipated Prescriber Population: The target population for trabectedin will be managed by prescribers who are familiar with the disease and adverse events such as bone marrow suppression and hepatotoxicity seen with drugs used for the treatment of advanced soft tissue sarcoma.

Anticipated Duration of Use: The proposed dose of trabectedin is 1.5 mg/m² body surface area (BSA) administered over 24 hours as an intravenous infusion once every 3 weeks until disease progression or unacceptable toxicity.

Patient labeling will be used to communicate the risk of neutropenia and elevated serum transaminases (ALT and AST) and the prescriber population likely to prescribe trabectedin will be comprised of physicians who are familiar with the disease and adverse events.

6 CONCLUSION

DRISK and DOP-2 concur that, at this time a REMS is not necessary to ensure that the benefits outweigh the risks for the proposed indication (b) (4)

The risks associated with trabectedin treatment will be communicated through professional labeling. Please keep DRISK informed if new safety information becomes available that would necessitate this benefit: risk profile to be re-evaluated.

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/s/

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