

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207953Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Yondelis (trabectedin)

Date: August 13, 2015

To: File for NDA 207953

From: John K. Leighton, PhD, DABT

Director, Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

I have examined pharmacology/toxicology supporting and labeling reviews for Yondelis conducted by Drs. Rosenfeldt, Gehrke, and Kufrin, and secondary memorandum and labeling provided by Dr. Helms. I concur with Dr. Helms' conclusion that Yondelis may be approved for the proposed indication.

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/s/

JOHN K LEIGHTON
08/13/2015

MEMORANDUM

Date: July 2, 2015
From: Whitney S. Helms, PhD.
Pharmacology Team Leader
Division of Hematology Oncology Toxicology for Division of Oncology Products 2
To: File for NDA #207953
Trabectedin (YONDELIS)
Re: Approvability of Pharmacology and Toxicology

Non-clinical studies examining the pharmacology and toxicology of trabectedin provided to support NDA 207953 for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have received a prior anthracycline-containing regimen were reviewed in detail by Hans Rosenfeldt, PhD, Brenda Gehrke PhD, and Dubravka Kufrin, PhD. The submission included studies of intravenously administered trabectedin in mice, rats, dogs, and monkeys that investigated the drug's pharmacology, pharmacokinetics, safety pharmacology, general toxicology, genetic toxicity (in vivo and in vitro), and reproductive toxicity. All studies required to support the approval of trabectedin were previously reviewed under NDA (b) (4) by Drs. Rosenfeldt and Gehrke; relevant portions of their review are included as appendices to the current NDA review.

Pharmacology studies demonstrating the mechanism of action of trabectedin are consistent with the use of alkylating drug as its established pharmacologic class. Trabectedin reversibly alkylates guanine residues at the exocyclic N2 position, causing the DNA to bend. While the exact mechanism of trabectedin is not fully characterized, the data suggests that trabectedin adducts stimulate transcription-coupled nucleotide excision repair and subsequently direct proteasome-dependent degradation of RNA polymerase II, resulting in eventual cell death.

In toxicology studies, the major targets of trabectedin mediated toxicity included the liver, kidney, spleen, bone marrow, pancreas, GI-tract, and skeletal and cardiac muscle. In addition injection site reactions occurred in all species. Necrosis was the predominant toxicity in all species, accompanied by immune infiltration particularly after the end of dosing. Hepatic, muscular, and injection site toxicities have been prominent findings in trabectedin-treated patients with liposarcoma and leiomyosarcoma as well.

During the original nonclinical review of trabectedin, the discovery of high levels of drug loss due to adsorption to some types of tubing was a serious complicating factor in the determination of exposure margins of the drug compared to human exposures. While this issue makes dose comparisons for some endpoints problematic, the animal studies did adequately demonstrate the toxicity profile for trabectedin. In pivotal repeat dose general toxicology studies in rats and monkeys the Applicant was able to estimate the actual trabectedin delivered dose based on concentrations before and after infusion and exposure margins in the trabectedin label are based on the corrected doses from these studies.

Trabectedin was both mutagenic and clastogenic in assays for genotoxicity. Carcinogenicity studies were not conducted to support the use of trabectedin in patients with unresectable or metastatic liposarcoma or leiomyosarcoma and are not warranted to support the use of the drug in these patients.

While studies to assess trabectedin-mediated effects on fertility were neither conducted nor required to support the approval of trabectedin for the treatment of patients with advanced cancer, histopathological findings in both rats and monkeys treated at doses lower than the recommended clinical dose suggest a potential for reduced male fertility following treatment with trabectedin. These findings are included in Section 13.1 of the trabectedin label. Because the drug is genotoxic, the label also includes a recommendation for males treated with trabectedin to use contraception (b) (4) 5 months, (b) (4) after the last dose of Yondelis.

Embryofetal development studies were performed in both rats and rabbits; however the highest nominal doses used in these studies were 0.01-0.02 times the 1.5 mg/m² dose recommended for patients due to maternal toxicity at higher doses and are, therefore, of limited value for assessing the potential for trabectedin-mediated reproductive toxicity. Trabectedin was able to cross the placenta in a placental transfer study and accumulated in the fetal liver at high levels for up to 24 hours following dosing. Despite the deficiencies of the submitted embryofetal development studies, based on its mechanism of action as alkylating drug that targets rapidly dividing cells, trabectedin has the potential to cause embryofetal harm and because of this, additional studies are not warranted to support the use of this drug in patients with advanced cancer. A warning for embryofetal risk and a recommendation for females to use contraception during and for up to 2 months following treatment with Yondelis are included in the label.

Recommendations: I concur with the conclusion of Drs. Rosenfeldt, Gehrke, and Kufirin that the pharmacology and toxicology data are sufficient to support the approval of NDA 207593 for YONDELIS for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have received a prior anthracycline-containing regimen. There are no outstanding nonclinical issues that would prevent the approval of YONDELIS for the proposed indication.

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/s/

WHITNEY S HELMS
07/02/2015

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 207953
Supporting document/s: 1
Applicant's letter date: November 24, 2014
CDER stamp date: November 24, 2014
Product: Trabectedin (Yondelis)
Indication: (b) (4) liposarcoma and leiomyosarcoma
Applicant: Janssen Products, LP
Review Division: Division of Hematology Oncology Toxicology in support of Division of Oncology Products 2 (DOP2)
Reviewer: Dubravka Kufrin, PhD
Supervisor/Team Leader: Whitney Helms, PhD
Division Director:

- John K. Leighton, PhD, DABT for DHOT, OHOP
- Patricia Keegan, MD for DOP2, OHOP

Project Manager: Anuja Patel

Disclaimer

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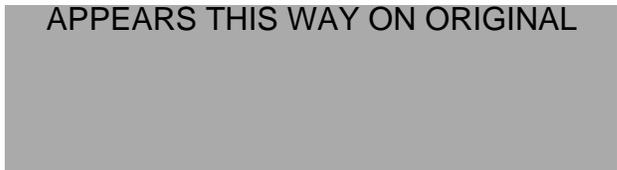
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1 Executive Summary

1.1 Introduction

Janssen has submitted a New Drug Application for trabectedin for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have received a prior anthracycline-containing regimen. The recommended dose of trabectedin is 1.5 mg/m² given as a 24-hour intravenous infusion once every 3 weeks.

All of the nonclinical studies required to support use of trabectedin in the proposed patient population were previously reviewed under NDA (b) (4) by Drs. Hans Rosenfeldt and Brenda Gehrke. Relevant portions of that review are appended to the current review as Appendices 1 and 2. The only new relevant nonclinical study submitted under the current NDA is Study PBC040-101: Placental and embryo fetal transfer study of 14C-et-743 in pregnant rats.

1.2 Brief Discussion of Nonclinical Findings

Trabectedin is small molecule alkylating drug consisting of three fused tetrahydroisoquinoline ring systems. The “A” and “B” subunits bind DNA, reversibly alkylate guanine at the exocyclic N² position, and bend DNA. Structural modeling suggests that the third “C” tetrahydroisoquinoline ring system protrudes out of the minor groove of DNA and has little interaction with DNA. Cell culture and xenograft experiments show that trabectedin is cytotoxic to a variety of tumor cell lines, including cell lines derived from sarcomas.

Pharmacokinetic studies with trabectedin in mice, rats, dogs, and monkeys showed that plasma levels of trabectedin decline rapidly after intravenous administration due to extensive tissue distribution. The half-life of trabectedin was 20 hours in rodents, and 40-230 hours (1.6-9.6 days) in monkeys, depending on dose. The terminal human half-life is 175 hours (7.3 days). In animals as well as in humans excretion of trabectedin was mostly biliary. In animal studies the greatest tissue concentration of trabectedin was in the liver, ranging from 15-35% of the total dose. The spleen, lung, mammary gland, bone marrow, kidney, muscle tissue, and pancreas also had significant concentrations of trabectedin. ET-729 is a major active human metabolite of trabectedin with toxicity profile that mimics the parent compound. ET-729 was also present in animals at adequate levels to cover its contribution to the toxicological profile of the drug.

The Applicant conducted toxicology studies in mice, rats, dogs, and monkeys to demonstrate the safety profile of trabectedin. Necrosis was the predominant toxicity noted in all species, often accompanied by inflammation in immunocompetent animals. Major target organs in all species included the liver and injection site. Injection site findings include thrombosis, fibrosis, necrosis, muscle degeneration, and inflammation. In rats, elevated bilirubin (up to 10 fold higher than levels seen in controls) occurred at nominal doses as low as 10 µg/kg (approximately 0.04 times the recommended dose in

humans based on body surface area). Findings in monkeys included liver necrosis and yellow skin. Large increases in liver enzymes, cholesterol and triglycerides occurred in both species. Toxicity in the liver and at injection sites persisted through the recovery period in many studies. Hepatotoxicity and severe injection site reactions have been reported clinically.

Additional target organs in animals correlated with the distribution of the drug and included the spleen, kidney, lung, pancreas, and gastrointestinal tract. The bone marrow and muscle, both skeletal and cardiac were also targets of trabectedin-mediated toxicity. Hypocellularity in the bone marrow was accompanied by decreases in red blood cells in both rats and monkeys and, in some cases, decreases in white blood cells at high dose levels. Increases in neutrophils were common in both species, likely secondary to tissue damage and injection site reactions. In general toxicology studies in monkeys, increases in plasma levels of creatine kinase and myoglobin were reported as well as histopathological findings of hemorrhage, necrosis, and thrombosis in the heart. Cardiac toxicity also occurred in rats with hemorrhage and inflammation noted in the heart at multiple dose levels. The potential for cardiovascular toxicity was further suggested in a hemodynamic study in the cynomolgus monkey which showed decreases in mean arterial blood pressure of up to 26% following administration of a single 1080 $\mu\text{g}/\text{m}^2$ dose of trabectedin. Skeletal muscle degeneration was noted in rats. Similarly, decreased muscle tone occurred with dose-dependent increases in frequency in monkeys. Rhabdomyolysis has been reported clinically in patients with sarcoma treated with trabectedin.

Trabectedin did not demonstrate a potential for causing QTc prolongation in either the in vitro hERG assay or in in vivo studies, consistent with the lack of QT prolongation in clinical studies. Trabectedin is both mutagenic and clastogenic based on positive results in an in vitro Ames assay, an in vitro chromosome aberration assay, and an in vivo mouse micronucleus assay. Carcinogenicity studies were not conducted and are not required to support the use of a drug intended for the treatment of patients with advanced cancer.

No dedicated fertility studies were conducted with trabectedin. In male rats histopathological signs of hemorrhage and diffuse degeneration of the germinal epithelium occurred in testes at doses $\geq 300 \mu\text{g}/\text{m}^2$ (approximately 0.2 times the human dose of 1.5 mg/m^2). At a trabectedin dose of 420 $\mu\text{g}/\text{m}^2$, monkeys presented with oligospermia/aspermia in the epididymis. Together, these findings suggest a potential for reduced male fertility following treatment with trabectedin.

Embryofetal development studies were conducted with trabectedin in both rats and rabbits. Due to maternal death in dose range-finding studies, very low doses of trabectedin were used in the definitive studies. Based on body surface area, the highest doses used in the definitive studies in rats (15 $\mu\text{g}/\text{m}^2/\text{day}$) and rabbits (24 $\mu\text{g}/\text{m}^2/\text{day}$) were .01 to .02 times the 1.5 mg/m^2 clinical dose and actual doses delivered to these animals may have been lower due to adsorption to the tubing. In the rat, maternal body weight and food consumption were decreased at the 15 $\mu\text{g}/\text{m}^2/\text{day}$ dose level;

decreased food consumption occurred in the rabbits administered 24 $\mu\text{g}/\text{m}^2/\text{day}$. While maternal toxicity was observed at these doses, there were no treatment-related effects on embryofetal survival or the incidence of malformations and variations in either rats or rabbits. Toxicokinetic analysis was not conducted in the embryofetal development studies; thus cross-species comparisons are based on dose and not exposure. In a placental transfer study conducted in pregnant rats treated with trabectedin, there was higher accumulation of trabectedin in the placenta and amnion than in maternal plasma. Trabectedin was also able to pass through the placenta, where it accumulated in the fetal liver at concentrations that exceeded those in maternal plasma and persisted until the end of the study (24 hours post dosing). Given that the highest doses used in the embryofetal development studies were significantly below the recommended human dose, they are of limited utility for assessing the reproductive risk of the drug; however, based on its mechanism of action as a genotoxic agent that targets rapidly dividing cells as well as its ability to pass through the placenta, the label for trabectedin should include a warning for embryofetal toxicity.

Trabectedin adsorbs preferentially to some infusion materials at high levels, particularly at low dose levels. This property of the drug, identified in the original review of NDA (b) (4) makes dose comparisons to human doses problematic for many nonclinical studies and has resulted in specific recommendations that are included in the "Preparation for Administration" section of the label. Despite this issue, the animal studies were adequate to demonstrate the toxicity of the drug. In addition, the Applicant (b) (4) specification for (b) (4) a single unqualified impurity identified in the original review, to an acceptable level based on ICH Q3B. At this level, no further toxicological qualification is required. There were no further outstanding pharmacology/toxicology issues regarding trabectedin that would prevent the approval of the drug for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma.

1.3 Recommendations

1.3.1 Approvability

The nonclinical studies submitted to this NDA provide sufficient information to support use of trabectedin for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma given as a 24-hour intravenous infusion at a dose of every 3 weeks.

1.3.2 Additional Non Clinical Recommendations

None.

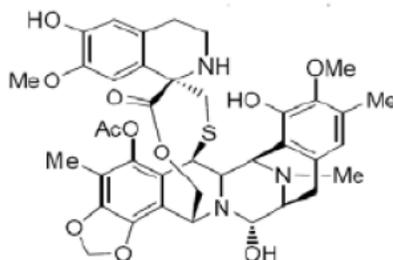
1.3.3 Labeling

A separate labeling review will be provided.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)	Not provided
Generic Name	Trabectedin (ecteinascidin 743)
Code Name	ET-743, R279741
Chemical Name	(6R,6aR,7R,13R,14S,16R,20R)-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-19-oxo-3',4',6,7,12,13,14,16-octahydro-2'H,6aH-spiro[7,13-epimino-6,16-(epithiopropanooxymethano) [1,3]dioxolo [7,8]isoquino [3,2-b][3]benzazocine-20,1'-isoquinolin]-5-yl acetate
Molecular Formula/Molecular Weight	C ₃₉ H ₄₃ N ₃ O ₁₁ S/ 761.84 g/mol



Structure or Biochemical Description

Pharmacologic Class Alkylating agent

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND (b) (4), IND 50286, DMF (b) (4)

2.7 Regulatory Background

Date	Summary of Interaction
23 Nov 2010	Type C meeting to discuss protocol for the NDA's pivotal trial ET743-SAR-3007
12 July 2012	Update at ovarian EOP2 led to FDA suggestion to share secondary PFS & ORR data from phase 3 study ET743-SAR-3007 as basis for possible accelerated approval

Date	Summary of Interaction
09 Jan 2014	Based on IDMC (dated 13 Dec 2013) recommendation Janssen Sponsor Committee submits interim OS and final PFS and ORR along with proposed independent review auditing plan for PFS endpoint
07 Jul 2014	Type C meeting to share audit results for PFS: <ul style="list-style-type: none"> • Results appear consistent with primary investigator-assessed PFS analysis • PFS effect similar in magnitude to a recent approval for STS • Could form the basis of accelerated/regular approval, depending upon how clinically meaningful, statistically persuasive, free from bias and risk-benefit profile

5 Pharmacokinetics/ADME

Study title: Placental and embryo fetal transfer study of ¹⁴C-ET-743 in pregnant rats

Study no.: PBC040-101 (13DA51)
 Study report location: Electronic submission tab
 Conducting laboratory and location: (b) (4)
 Date of study initiation: December 11, 2013
 GLP compliance: No, not specified
 QA statement: Yes
 Drug, lot #, and % purity: Trabectedin, (b) (4), 98.5% with ¹⁴C-ET-743

Methods

Doses: 0.061 mg/kg
 Frequency of dosing: single administration
 Route of administration: IV
 Dose volume: 5 mL/kg

Formulation/Vehicle: Trabectedin (b) (4) in ¹⁴C-ET-743, (b) (4)

Species/Strain: Rat, Crl:CD(SD), female
 Number/Sex/Group: 3 females per sampling time
 Age: 9 weeks
 Weight: 304.13-374.96 g
 Satellite groups: None
 Unique study design: No

Group	Dosing route	Dose Dosing volume	Sampling time after administration	Number of animals dosed (Animal No.)
1	Intravenous	0.061 mg/kg 5 mL/kg	0.5 hours	3 (111 to 113)
			1 hour	3 (121 to 123)
			2 hours	3 (131 to 133)
			8 hours	3 (141 to 143)
			24 hours	3 (151, 152, and 154)

To avoid the risk of incomplete pregnancy or delivery, surplus animal (reserve animal numbers 2) was administered.

(Excerpted from Applicant's submission)

Blood, plasma, placenta, amnion, and amniotic fluid were sampled from dams. 7 tissues were sampled from fetuses: blood, brain, heart, lung, liver, kidney, and whole body.

Summary

Pregnant rats were administered a single IV of dose of ¹⁴C-ET-743 at 0.061 mg/kg to measure the placental and embryo fetal transfer of ET-743 in rats.

Table 1: Radioactivity concentration in plasma and blood

Tissue	Radioactivity concentration (ng eq./mL or g)									
	0.5 h		1 h		2 h		8 h		24 h	
Plasma	3.73	± 0.56	2.45	± 0.38	1.44	± 0.22	0.633	± 0.102	ND	
Blood	6.56	± 1.15	4.45	± 0.59	2.88	± 0.14	ND		ND	
Placenta	60.8	± 8.1	57.0	± 3.3	59.5	± 7.8	49.1	± 2.7	38.4	± 4.0
Amnion	25.2	± 4.3	30.6	± 3.1	36.5	± 12.1	40.6	± 6.2	36.6	± 11.3
Amniotic fluid	ND		ND		ND		ND		ND	
Fetus	1.86	± 0.61	2.48	± 0.36	2.56	± 0.45	2.35	± 0.75	2.48	± 0.15
Fetal blood	ND		ND		ND		ND		ND	
Fetal brain	ND		ND		ND		ND		ND	
Fetal heart	ND		ND		ND		ND		ND	
Fetal lung	2.55	± 0.46	3.21	± 0.58	3.22	± 0.49	3.80	± 0.62	3.17	± 0.24
Fetal liver	4.61	± 0.31	5.13	± 0.69	6.73	± 1.26	6.21	± 0.79	7.04	± 1.11
Fetal kidney	ND		ND		ND		ND		ND	

Data were the mean ± SD of the results from three animals.

ND: Not detected

(Excerpted from Applicant's submission)

The highest trabectedin-related radioactivity was observed in the placenta at 0.5 hours after administration, with placental concentrations that were 9 to 17 times higher than those in blood and plasma, respectively. The concentrations in the fetal liver and fetal lung were similar to levels seen in maternal plasma at 0.5 hours post dosing; however, while no radioactivity was detected in maternal plasma and blood 24 hours after dosing, test-article concentrations increased in fetus, specifically in fetal liver and lung, increased within the first hour and persisted until the final 24 hours post-administration collection.

Conclusions

- The radioactivity distributed to the placenta and amnion was higher than that in maternal plasma
- ET-743 can pass through the placenta, and persists, especially in fetal liver

12 Appendix/Attachments

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 207953

Applicant: Janssen Products, LP

**Stamp Date: November 24
2014**

**Drug Name: Yondelis
(trabectin)**

NDA Type: 505(b)(1)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	Yes		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	Yes		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	Yes		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	Yes		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	Yes		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	Yes		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	Yes		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Yes		An additional toxicology study was proposed for qualification of impurity ^{(b) (4)} threshold, but

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
				instead, the manufacturer (b) (4) this impurity specification to no more than (b) (4). The additional study, is, therefore, not required.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	Yes		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	Yes		The specification for impurity (b) (4) No additional toxicology studies needed for ET-745.
11	Has the applicant addressed any abuse potential issues in the submission?			
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Dubravka Kufrin -S (Affiliate) Digitally signed by Dubravka Kufrin -S (Affiliate)
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300403796, cn=Dubravka Kufrin -S (Affiliate)
Date: 2015.01.13 09:11:51 -05'00'

Reviewing Pharmacologist

Date

Team Leader/Supervisor

Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

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/s/

DENALI D KUFRIN
01/13/2015

WHITNEY S HELMS
01/13/2015