

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201525Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 201525
Supporting document/s: 1
Applicant's letter date: 09/15/2010
CDER stamp date: 09/17/2010
Product: Docetaxel Injection
Indication: BC, NSCLC,HRPC,GC,SCCHN
Applicant: Sandoz Inc.
506 Carnegie Center, Ste 400
Princeton, NJ 08540
Review Division: Division of Drug Oncology Products
Reviewer: G. Sachia Khasar, Ph.D.
Supervisor/Team Leader: Whitney Helms, Ph.D. (Acting)
Division Director: Robert Justice, M.D., M.S.
Project Manager: Jamila Mwidau, BSN, RN, MPH

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 201525 are owned by Sandoz, Inc. or are data for which Sandoz, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 201525 that Sandoz, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 201525.

MEMORANDUM

- A. Recommendation on approvability: Approve as 505(b)(2).
- B. Recommendation for nonclinical studies: None.
- C. Recommendations on labeling: The content of the pharmacology/toxicology sections are the same as those of the reference listed drug.

September 17, 2010, Sandoz submitted NDA 201525 in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, with a proposal for a ready to use Docetaxel Injection (10 mg/mL) in the following presentations: 20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL. The proposal is based on Taxotere® (docetaxel) Injection concentrate ((NDA 20449) the reference listed drug (RLD)), initially approved in 1996 and marketed by Sanofi-Aventis. The Sandoz-proposed Docetaxel Injection 10 mg/mL contains the same active ingredient as the RLD, however, it differs from the RLD in that it contains less polysorbate 80 and more 96% ethanol. In addition, Sandoz Docetaxel Injection contains polyethylene glycol 300 as solubilizer and anhydrous citric acid for pH adjustment. The comparison of Sandoz docetaxel and the RLD as well as the Sandoz docetaxel injection formulation are shown below.

(Excerpted from the sponsor's submission).

	Proposed Ebewe Drug Product (Docetaxel) 10mg/mL	Reference Listed Drug (Taxotere) 40 mg/mL Base (10mg/ml after dilution)
Active	Docetaxel	Docetaxel
Excipients	Polysorbate 80	Polysorbate 80
	Polyethylene glycol 300	N/A
	Ethanol 96% (v/v)	N/A
	Citric Acid, anhydrous	N/A
Diluent	N/A	13% Ethanol in water for injection solution

Ingredient	Function	20mg/2mL	80mg/8mL	160mg/16mL
Docetaxel	Active	20.0 mg	80.0 mg	160.0 mg
Polysorbate 80, USP				(b) (4)
Polyethylene Glycol 300, USP				
Ethanol 96%, USP (v/v)				
Citric Acid Anhydrous, USP				
				(b) (4)

Sandoz Docetaxel Injection, 10 mg/mL, is a sterile, non-aqueous ready to use solution intended for infusion after dilution. Docetaxel Injection 10 mg/mL is available as 20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL. Each 1 mL contains 10 mg docetaxel, 80 mg polysorbate 80, 648 mg polyethylene glycol 300, 275.9 mg ethanol 96% (v/v), and 4 mg anhydrous citric acid.

No non-clinical data were submitted with this application. The application relies on data submitted with NDA 20449, owned by Sanofi-Aventis.

Impurities

The following is excerpted from response to the pre-NDA meeting questions communicated to the sponsor on June 26, 2008

Section 2.1, Question

E. Preliminary stability studies of the Ebewe Pharma ready to use (RTU) formulation has shown the presence of the degradant (b) (4). This degradant is also present in the innovator product but only after reconstitution. Since the Ebewe Pharma product is a RTU formulation this degradant is seen sooner in the Ebewe Pharma product and also at a slightly higher level than the innovator product. Testing of Taxotere® by Ebewe Pharma has been performed and the results for (b) (4) were (b) (4). The Ebewe Pharma product has also been tested and at 2 months stability the result was (b) (4). Ebewe Pharma is proposing a release limit of NMT (b) (4) and a stability limit of NMT (b) (4).

Non-clinical toxicity studies have been conducted to qualify the degradant, (b) (4) by the NDA holder of Taxotere® NDA #020449. These studies include a *in vitro* cytotoxicity study in P388 leukaemic cells and an *in vivo* efficacy study in B16 melanoma-bearing mice, as well as a single-dose toxicity and a five day repeat-dose toxicity study in mice. The former data were used to define the efficacy of the degradant with respect to the docetaxel drug substance, while the latter were used to support a degradation limit of up to (b) (4) proposed by the Taxotere® applicant. Ebewe Pharma has conducted an extensive literature search for the (b) (4) degradant and would like to use published literature to support the presence of (b) (4) in the product as well as to justify the proposed limits.

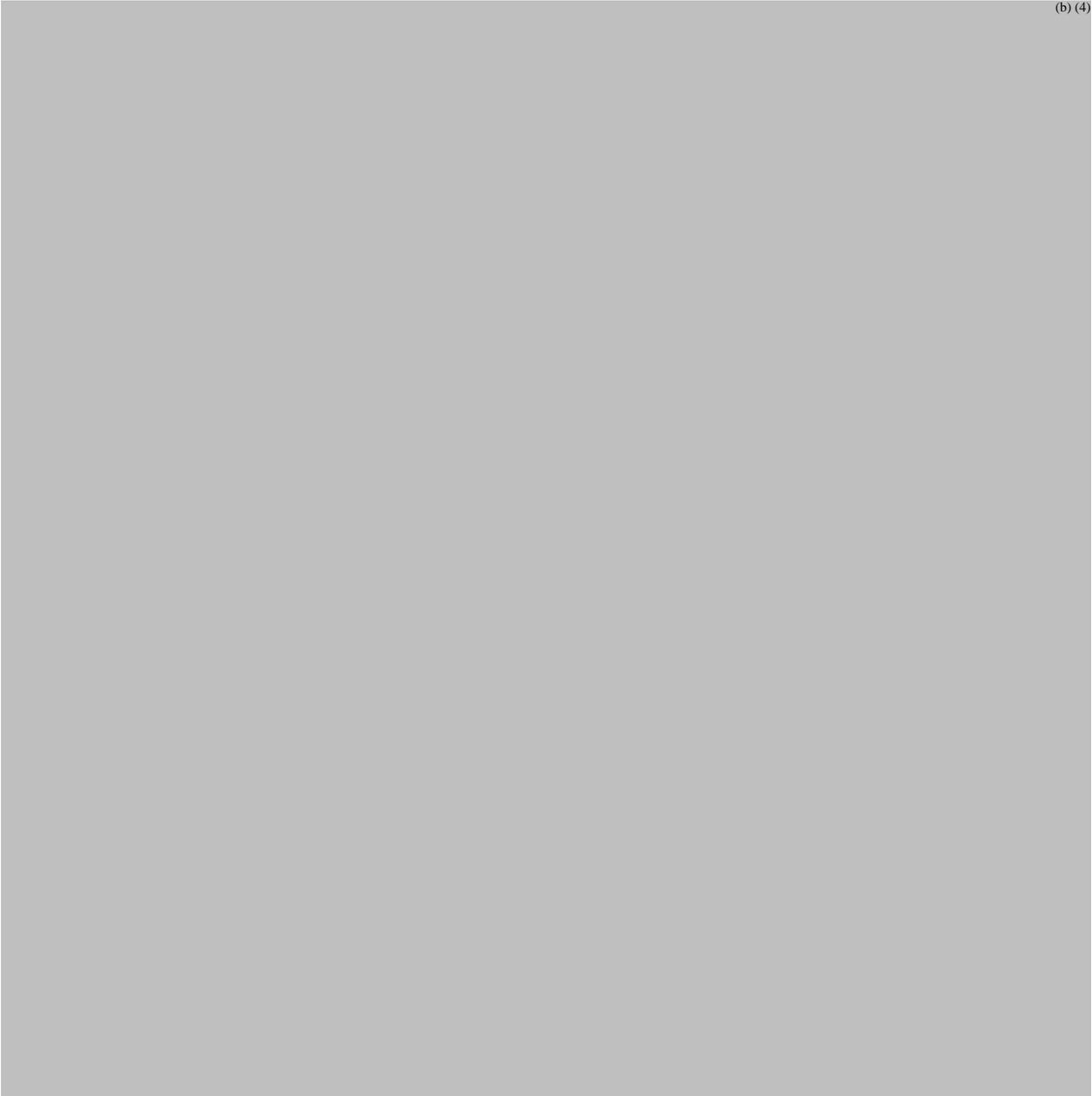
Does the Agency agree with the use of published literature to support the (b) (4) impurity?

FDA Response: You should include a side by side comparison of 3 batches of listed drug close to expiry with 3 batches of your drug product using your analytical methods. If the comparison indicates significant difference in the impurity profiles and if any of those impurities exceed ICH Q3B(R2) in your product then those impurities need to be adequately qualified. All chemical structures exceeding identity threshold should be clearly identified.

If you believe previously conducted toxicology studies used for impurity justification of the RLD can be used to justify your impurity specification of (b) (4) for (b) (4), you will need to provide the complete studies, as well as drug lots, analytical data, and related chemical structures of the tested impurities. Additional studies may be required following review of the submitted data.

Alternatively, you may conduct a single-dose study in mice bridging the RLD to Docetaxel Injection (mice appear to be more sensitive to the neurotoxic effects of taxanes). All individual impurity concentrations of batches of tested Docetaxel Injection must equal or exceed the maximum shelf-life specifications to be used clinically. The preclinical study will set the limit for impurities.

The sponsor was advised to provide data to justify the specification of (b) (4) for (b) (4) or conduct a bridging study. The sponsor mentioned studies conducted by the RLD sponsor to qualify up to (b) (4). As it is, the (b) (4) specification exceeds the limit for both the RLD and that required by ICH Q3B(R2).



Considering the extensive clinical experience with taxotere, (b) (4) is qualified from a toxicological perspective. Moreover, (b) (4) found that docetaxel metabolites were markedly less cytotoxic and myelotoxic than the parent compound. Therefore, (b) (4) is considered qualified from a pharmacology/toxicology perspective.

(b) (4)
The CMC reviewer alerted the pharmacology/toxicology reviewer of the presence of (b) (4) in the drug substance (DS) at a specification of (b) (4) is not listed in ICH Q3C. Therefore, the sponsor was asked to justify the presence of (b) (4).



(b) (4)

The sponsor has proposed a specification of (b) (4) for (b) (4) in the drug substance. At the proposed specification, given a dose of (b) (4) of docetaxel injection every 3 weeks, the amount of (b) (4) administered would be (b) (4) every 3 weeks, a dose which is well below the NOEL even for daily administration. Considering a $t_{1/2}$ of 3.8 hours, it is unlikely that this amount of (b) (4) would pose a significant risk to humans. Therefore, from Pharmacology/Toxicology perspective, (b) (4) of (b) (4) in the drug substance appears to be acceptable.

Conclusion

Although the specification for (b) (4) in the proposed Sandoz docetaxel formulation exceeds that in the RLD, (b) (4) is a metabolite of docetaxel. Considering the extensive clinical experience with taxotere, (b) (4) is considered qualified from a toxicological perspective. Similarly, (b) (4) is not expected to pose a significant risk to humans. Labeling of the non-clinical sections is the same as the RLD. Therefore, there are no pharmacology/toxicology issues which preclude approval of Docetaxel Injection as a 505(b)(2).

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/s/

GABRIEL S KHASAR
06/09/2011

WHITNEY S HELMS
06/09/2011

MEMORANDUM

Date: June 8, 2011
From: Whitney S. Helms, Ph.D.
Acting Supervisory Pharmacologist
Division of Drug Oncology Products
To: File for NDA #201525
Docetaxel Injection
Re: Approvability of Pharmacology and Toxicology

Sandoz Inc. submitted a 505(b)2 NDA application for the treatment of patients with breast cancer, non-small cell lung cancer (NSCLC), hormone refractory prostate cancer, gastric carcinoma, or squamous cell carcinoma of the head and neck cancer. The reference listed drug for this product is Taxotere™. No new nonclinical studies were submitted to support this application. Two issues came up during the review process that required input from the pharmacology/toxicology team.

As a result of a change in formulation between the RLD and the Sandoz product, there was an increase in the level of the (b) (4) impurity. At a pre-NDA meeting with the company, the FDA informed Sandoz that if the levels of impurity were higher than those of the RLD then an additional nonclinical study might be required for qualification. During the interim between the pre-NDA meeting and the review of the NDA, however, there was a publication showing that (b) (4) is a metabolite of docetaxel and is found at high levels in human plasma. Thus, the sponsor was not required to do further qualification studies for this impurity. The sponsor was also asked to justify the (b) (4) specification level for (b) (4) in their product. The sponsor provided data from the literature to show that the level of clinical (b) (4) exposure resulting from administration of Sandoz docetaxel is significantly lower than the documented no observed effect level (NOEL) in 2 species, thus, the specification was considered to be justified.

Recommendations: I concur with Dr. G. Sachia Khasar's conclusion that the level of (b) (4) in the Sandoz product does not require further qualification despite being higher than the RLD because the impurity has been shown to be a human metabolite. In addition, the sponsor has provided sufficient data to justify the level of (b) (4) in their product. This 505(b)2 product is, therefore, approvable from a pharmacology/toxicology perspective.

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/s/

WHITNEY S HELMS
06/09/2011

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 201,525

Applicant: Sandoz, Inc.

Stamp Date: 09/17/2010

Drug Name: Docetaxel
Injection

NDA Type: 505 (b)(2)

On **initial** overview of the NDA 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?	N/A		Non-clinical study data were not submitted.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	N/A		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	N/A		
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)?	N/A		
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).	N/A		
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?	N/A		
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?	N/A		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	N/A		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA**

	Content Parameter	Yes	No	Comment
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.)		No	No impurity issues have been identified to date
11	Has the applicant addressed any abuse potential issues in the submission?	N/A		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	N/A		

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

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

None

G. Sachia Khasar, Ph.D. 10/27/2010

 Reviewing Pharmacologist Date

S. Leigh Verbois, Ph.D. 10/28/2010

 Team Leader/Supervisor Date

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/s/

GABRIEL S KHASAR
10/29/2010

SANDI L VERBOIS
10/29/2010