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APPLICATION NUMBER:

203551Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

DATE	14-MAR-2013
From	Nallaperumal Chidambaram, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	203551
Applicant	Actavis, Inc.
Date of Submission	14-MAR-2012
PDUFA Goal Date	14-APR-2013
Proprietary Name/ Established (USAN) names	Docetaxel Injection
Dosage forms / Strength	20 mg/1 mL, 80 mg/4 mL, and 140 mg/7 mL
Proposed Indication(s)	1. Breast cancer 2. Non-small cell lung cancer 3. Prostate cancer 4. Gastric adenocarcinoma 5. Head and neck cancer
Recommendation:	Approval

1. Introduction

NDA 203551 was submitted in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act on 14-Mar-2012. This CDTL memo serves to summarize the critical issues noted in all review disciplines and recommends “**Approval**” action for this application. All individual discipline reviews may be found in DARRTS.

2. Background

Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into microtubules and inhibits their disassembly which then leads to a marked decrease of free tubulin. The Reference Listed Drug for this submission is the two-vial formulation of Taxotere® (docetaxel) Injection Concentrate (NDA 20-449). The currently approved one-vial reference listed drug was approved after the development of this drug product formulation was completed, so the applicant used the two-vial Taxotere product as their reference product. The one-vial and two-vial reference listed drug products are marketed by Sanofi Aventis. The proposed drug product is a concentrate in one vial that is diluted for intravenous administration. Docetaxel Injection is supplied in three presentations (20 mg/1 mL, 80 mg/4 mL and 140 mg/7 mL). All three strengths are dose proportional. The proposed drug product is

formulated with citric acid, (b)(4), Povidone (Kollidon 12 PF) as a (b)(4), Polysorbate ((b)(4)) and ethanol as (b)(4).

Dosing Regimen and Administration

Multiple indications and dosing regimens are associated with this NDA. Please refer to the Medical Officer's 14-JAN-2013 review for additional details.

3. CMC

General product quality considerations

The CMC reviewer (Dr. Xiao Hong Chen) in her review dated 22-FEB-2013 recommended approval of this application from her perspective.

The proposed formulation contains Povidone K 12. This excipient is currently used in a number of FDA and EU approved intravenous drug product formulations (including docetaxel product marketed in Europe). In addition, the applicant provided adequate nonclinical data to support the use of this excipient in the formulation. The nonclinical review team was consulted to evaluate safety concerns due to the amount of povidone in the formulation. The nonclinical reviewer/team determined that the amount of povidone in the formulation is acceptable from a safety perspective.

The formulation also contains 40% ethanol, the amount of ethanol that is provided in the formulation is quite high and therefore this cannot be considered a residual solvent. The amount is higher than ICH Q3C recommended levels under Option 1 (400,000 ppm vs. ICH limit of 5000 ppm) or Option 2 (80 mg vs. ICH limit of 50 mg/day). The highest amount of ethanol content in an FDA approved drug product was found to be 15%, in (b)(4). The pharm/tox review team was consulted to evaluate for safety concerns for this high an amount of ethanol. The nonclinical reviewer/team concluded no safety concern based on comparative toxicology study and on the nature of the excipient (ethanol).

The osmolarity values proposed for the drug product was also determined to be approximately twice that of the two-vial reference listed drug. At Agency's request, the applicant provided experimental as well as calculated osmolarity values for both the US 1-vial, EU 1-vial and 2-vial formulations. Minor differences in the formulation were noted between the US 1-vial (absence of citric acid) and EU 1-vial formulation, and that did not result in substantial difference in osmolarity values (1 mOsm/L). Osmolarity values between the proposed formulation and US 1-vial formulation were found to be comparable. The clinical team determined that there was insufficient data for this theoretical risk to warrant any

change in safety or administration of the drug (refer to medical Officer's review dated 14-JAN-2013).

ONDQA Biopharm review

The Biopharm reviewer (Dr. Elsbeth Chikhale) noted in her review dated 24-NOV-2012 that the active ingredient in this submission is an anhydrous form of docetaxel and the RLD is a trihydrate. However, both the formulations are diluted to 0.74 mg/mL before infusion. Similarly, the current and the referenced formulation are micelle containing solutions that are comparable in size.

The Biopharm reviewer further noted that per CFR 320.22(b), for certain drug products the *in vivo* bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement from submitting *in vivo* BA/BE data for these drug products. A drug product's *in vivo* bioavailability or bioequivalence may be considered to be equivalent if the drug product meets the following criteria: If the drug product is a parenteral solution intended solely for administration by injection, and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved new drug application or abbreviated new drug application. It should be noted that the inactive ingredients in the current formulation are different from the referenced listed formulation; however, both the products are parenteral solutions for intravenous administration. The concentration of the active ingredient (docetaxel) remains the same, and it has the same route of administration. The osmolarity values were also found to be different between the current 1-vial and referenced 2-vial formulation. The differences in pH are not expected to affect the bioavailability of the current docetaxel product. The reviewer concluded that though CFR requires the active and inactive ingredients for a 505(b)(2) application to be the same as the referenced product, the differences that are noted above with respect to the inactive ingredients are not expected to affect the amount of drug delivered at the site of action, additionally, the drug product is an injectable administered by intravenous infusion. Therefore, the *in vivo* BA/BE of the current docetaxel injection is self-evident and the applicant's request to waive the *in vivo* bioequivalence study requirement was found to be acceptable. The Biopharm reviewer recommended approval of this application from her perspective.

Facilities review/inspection

The Office of Compliance provided an overall acceptable recommendation on 08-Jan-2013 (D. Smith).

Microbiology

The microbiology reviewer (Mr. S. Donald) recommended approval of this application from his perspective on 31-OCT-2012.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer (Dr. Wei Chen) in her review dated 26-FEB-2013 noted that a comparative toxicity study including a toxicokinetic study was conducted in rats with docetaxel concentrate and Taxotere. A toxicity study of Kollidon 12 PF using intravenous route was also conducted in rats. In addition, other nonclinical studies including pharmacology and *in vivo* protein binding studies were also conducted. The nonclinical reviewer/team found the above acceptable and therefore no new nonclinical studies were requested. The nonclinical review team recommended approval from their standpoint.

5. Clinical Pharmacology

The Clinical Pharmacology reviewer (Dr. Jeanne Fourie Zirkelbach) in her review dated 28-NOV-2012 noted granting of a waiver by ONDQA from conducting a bioequivalence study per 21 CFR 320.22(b)1. Minor labeling comments were noted. The clinical pharmacology reviewer/review team recommended approval of this application from their perspective.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Not applicable.

8. Safety

Not applicable.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics, Geriatrics, and Special Populations

Not applicable

11. Other Relevant Regulatory Issues

Application Integrity Policy (AIP): This application is not in the AIP list.
Exclusivity or patent issues of concern: No issues were noted for this NDA.

Financial disclosures: None submitted or needed

Other GCP issues: None

DSI audits: Not applicable

Other discipline consults: None

Environmental Assessment: The OPS reviewer (Dr. Raanan Bloom) noted in his review dated 14-JAN-2013 that the raw material is derived from cultivated plant sources. Based on provided information, the Agency has determined that no extraordinary circumstances exist for this application. Therefore, this application qualifies for a categorical exclusion under 21 CFR 25.31(a).

Any other outstanding regulatory issues: None

12. Labeling

Carton and container labels, and package insert were reviewed by DMEPA on 11-NOV-2012 and 13-FEB-2013 respectively and the reviewer (J. Schlick) found the labels and labeling acceptable.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

This reviewer recommends **Approval** for this NDA.

Risk Benefit Assessment

The review of this NDA is based primarily on chemistry, manufacturing and controls data. The applicant satisfactorily addressed all deficiencies and information requests and that there is no pending information request. In addition, the Office of Compliance provided an overall acceptable recommendation for the manufacturing and testing facilities.

Recommendation for Postmarketing Risk Management Activities

This does not apply to this NDA.

Recommendation for other Postmarketing Study Commitments

None

Recommended Comments to Applicant

None.

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/s/

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03/15/2013