CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203551Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Submission Number	203551
Submission Code	000
Letter Date	Mar 14, 2012
Stamp Date	Mar 14, 2012
PDUFA Goal Date	Jan 14, 2013
Reviewer Name	Paul G. Kluetz, M.D.
Clinical Team Leader	V. Ellen Maher, M.D.
Review Completion Date	2012-Jan 3
Established Name	docetaxel
Trade Name	Docetaxel Injection Concentrate
Reference NDA	203551
Therapeutic Class	Microtubule disregulator and antineoplastic
Applicant	Actavis, Inc.
Priority Designation	Standard
Formulation	IV
Dosing Regimen	Multiple (see product information, 2.1)
Indication	Multiple (see product information, 2.1)
Intended Population	Multiple (see product information, 2.1)

Table of Contents

List of Tables

Reference ID: 3244624

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This NDA for docetaxel injection, in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, was submitted to request approval of therapeutic equivalence of the proposed product to Taxotere, as defined in the FDA orange book. The sponsor of NDA 20449 for Taxotere is Sanofi-Aventis. The exclusivity of the indications below have expired.

Breast Cancer

- Docetaxel Injection is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.
- Docetaxel Injection in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

Non-Small Cell Lung Cancer

- Docetaxel Injection as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.
- Docetaxel Injection in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

Prostate Cancer

- Docetaxel Injection in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

Gastric Adenocarcinoma

- Docetaxel injection in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

Head and Neck Cancer

- Docetaxel injection in combination with cisplatin and fluorouracil is indicated for induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

No new clinical data was submitted for this NDA. The Taxotere NDA 20449 has been previously reviewed for efficacy and safety. Therefore, the medical reviewer recommends approval (if pharmacological equivalence is established) for all of the above indications.

Reference ID: 3244624

1.2 Risk Benefit Assessment

Please refer to NDA 20449.

2 Introduction and Regulatory Background

Product Information
Established Name: docetaxel

Proprietary Name: Docetaxel Injection Concentrate 20mg/ml

Applicant: Actavis Inc.
60 Columbia Road Bldg B
Morristown, NJ 07960
Joann Stavole

Drug Class: Microtubule disregulator and antineoplastic

Proposed Indications:

Breast Cancer
Docetaxel injection concentrate is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

Docetaxel injection concentrate in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

Non-Small Cell Lung Cancer
Docetaxel injection concentrate as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.

Docetaxel injection concentrate in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

Prostate Cancer
Docetaxel injection concentrate in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

Gastric Adenocarcinoma
Docetaxel injection concentrate in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

Reference ID: 3244624

Head and Neck Cancer
Docetaxel injection concentrate in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Proposed Dosage and Administration

Breast Cancer
For locally advanced or metastatic breast cancer after failure of prior chemotherapy, the recommended dose of docetaxel injection concentrate is 60 mg/m^2 to 100 mg/m^2 administered intravenously over 1 hour every 3 weeks.
For the adjuvant treatment of operable node-positive breast cancer, the recommended docetaxel injection concentrate dose is 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 courses.

Non-Small Cell Lung Cancer
For treatment after failure of prior platinum-based chemotherapy, docetaxel injection concentrate was evaluated as monotherapy, and the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks.
For chemotherapy-naïve patients, docetaxel injection concentrate was evaluated in combination with cisplatin. The recommended dose of docetaxel injection concentrate is 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30 to 60 minutes every 3 weeks.

Prostate Cancer
For hormone-refractory metastatic prostate cancer, the recommended dose of docetaxel injection concentrate is 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion. Prednisone 5 mg orally twice daily is administered continuously.

Gastric Adenocarcinoma
For gastric adenocarcinoma, the recommended dose of docetaxel injection concentrate is 75 mg/m^2 as a 1 hour intravenous infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3 hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m^2 per day given as a 24-hour continuous intravenous infusion for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks.

Head and Neck Cancer
Induction chemotherapy followed by radiotherapy For the induction treatment of locally advanced inoperable SCCHN, the recommended dose of docetaxel injection concentrate is 75 mg/m^2 as a 1 hour intravenous infusion followed by cisplatin 75 mg/m^2 intravenously over 1 hour, on day one, followed by fluorouracil as a continuous intravenous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy.

Reference ID: 3244624

Induction chemotherapy followed by chemoradiotherapy For the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN, the recommended dose of docetaxel injection concentrate is 75 mg/m^2 as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3 hour infusion, followed by fluorouracil 1000 mg/m^2/day as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles.

Reviewer: The applicant has applied for all currently labeled indications on the Taxotere label.

Premedication Regimen

- Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice a day) for 3 days starting 1 day before administration

- HRPC: oral dexamethasone 8 mg at 12, 3, and 1 hr before treatment

For dosage adjustments during treatment see full prescribing information.

Dosage Forms and Strengths

Docetaxel Injection Concentrate is available as 20 mg/mL, 80 mg/4 mL and 140 mg /7 mL. Each mL contains 20 mg docetaxel, citric acid anhydrous (6 mg), kollidon 12 PF (povidone K12) (100 mg), polysorbate 80 (424 mg) and ethanol (400 mg/mL).

Contraindications

- Docetaxel injection concentrate is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Severe reactions, including anaphylaxis, have occurred *[see Warnings and Precautions (5.4)]*.
- Docetaxel injection concentrate should not be used in patients with neutrophil counts of <1500 cells/mm^3.

Warnings and Precautions

- Acute myeloid leukemia: In patients who received docetaxel injection concentrate, doxorubicin and cyclophosphamide, monitor for delayed myelodysplasia or myeloid leukemia (5.6)
- Cutaneous reactions: Reactions including erythema of the extremities with edema followed by desquamation may occur. Severe skin toxicity may require dose adjustment (5.7)
- Neurologic reactions: Reactions including. paresthesia, dysesthesia, and pain may occur. Severe neurosensory symptoms require dose adjustment or discontinuation if persistent. (5.8)
- Asthenia: Severe asthenia may occur and may require treatment discontinuation. (5.9)

- Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant when receiving docetaxel injection concentrate (5.10, 8.1)

Adverse Reactions
The most common adverse reactions across all docetaxel injection concentrate indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

Availability of Proposed Active Ingredient in the United States
Taxotere (NDA 20449) is marketed in the US.

Other approved docetaxel formulations include:
NDA 022234 Docetaxel Injection Hospira, Inc. 3/8/2011
NDA 022534 Docefrez Injection Sun Pharma Global 5/3/2011
NDA 201195 Docetaxel Injection Accord Healthcare, Inc 6/8/2011
NDA 201525 Docetaxel, Sandoz, 6/29/2011
NDA 022312 Docetaxel Injection, Apotex, Inc., 1/11/2012

2.1 Summary of Presubmission Regulatory Activity Related to Submission

There was no IND for this formulation

MAR 25, 2011, Pre-NDA meeting held.

In this meeting it was noted by FDA that at the time of the NDA submission that the applicant should provide nonclinical data that qualify the safety of povidone (Kollidon PF-12) for intravenous use at the concentration present in a dose of 100 mg/m^2 docetaxel injection concentration (i.e. 810 mg for a 60 kg person with a total body surface area of 1.62 mg/m^2).

MAR 14, 2012: Actavis submits NDA 203551

2.2 Pediatric Waiver

A pediatric waiver request was submitted with the NDA 203551 submission. The waiver is granted based on the very low incidence of pediatric patients with breast cancer, lung cancer, prostate cancer, or gastric cancer.

2.3 Other Relevant Background Information

Refer to NDA 20449

Reference ID: 3244624

Table 1: Patent Data for TAXOTERE Injection Concentrate

Patent Number	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Certification	21 CFR Reference
4814470	14 May 2010	X	X	Paragraph II	314.50(i)(1)(i)(A)(3)
5438072	22 Nov 2013	X		Paragraph IV	314.50(i)(1) (i)(A)(4)
5698582	03 Jul 2012	X		Paragraph IV	314:50(i)(1)(i)(A)(4)
5714512	03 Jul 2012	X		Paragraph IV	314.50(i)(1)(i)(A)(4)
5750561	03 Jul 2012	X		Paragraph IV	314.50(i)(1)(i)(A)(4)

Table 2: Exclusivity Data* for TAXOTERE Injection Concentrate

Exclusivity Code	Exclusivity Definition	Exclusivity Expiration
I-429	For use in combination with prednisone for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.	19 May 2007
I-436	For use in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer.	18 Aug 2007
I-490	For use in combination with Cisplatin and 5-FU for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of prior chemotherapy for advanced disease	Mar 22,2009
I-519	For use in combination with Cisplatin and 5-FU in patients with inoperable HNSCC prior to definitive treatment.	OCT 17,2009
I-542	Expansion of patient population for head and neck cancer from “inoperable” patients to all patients.	SEP 28,2010
I-543	For use in combination with Cisplatin and 5-FU in patients with advanced HNSCC prior to definitive treatment.	SEP 28,2010

* No exclusivity information remains in Orange Book for NSCLC indication.

The Pediatric exclusivity (code M-61) does not expire until 5/13/2013. All other indications have expired. The applicant has removed from their proposed labeling pediatric information that is protected under M-61.

3 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to NDA 20449 CMC, Pharmacology/Toxicology, and Clinical Pharmacology reviews, NDA 22534 CMC review, and the label.

4 Sources of Clinical Data

Refer to NDA 20449.

5 Review of Efficacy

Refer to NDA 20449.

Reference ID: 3244624

6 Review of Safety

Refer to NDA 20449.

Additional Review Issues:

Osmolarity:
The clinical review team initially noted that the osmolarity of the proposed docetaxel concentrate by Actavis was approximately twice as high as the 2-vial Taxotere reference product. While the osmolarity (597-687 mOsmol/L) is higher than the 2-vial Taxotere product, it has been determined that the reference product Taxotere is now solely distributed in the 1-vial formulation in the U.S. which has comparable osmolarity to the applicant's product.

There is a theoretical risk that the increase in osmolarity may provide a slight increase in the risk for venous irritation or thrombophlebitis. It appears that the theoretical risk of peripheral venous irritation or thrombophlebitis based on a 250 mL solution of approximately 600 mOsmol/L infused over 1 hour and given with dexamethasone pretreatment is very small. The clinical team determined that there was insufficient data for this theoretical risk to warrant any change in safety or administration labeling.

Use of Povidone K12:
It was noted that the formulation for Actavis docetaxel utilizes povidone K12. This excipient was discussed in the pre-NDA meeting held in 3/2011. The applicant submitted sufficient non-clinical data to the FDA to support the use of povidone for this formulation (see nonclinical toxicology review). Povidone is currently used as an excipient in several U.S. and European intravenous drug formulations (including a docetaxel product marketed in Europe). It was determined by the clinical review team in consultation with the nonclinical reviewers that the concentration of povidone K12 used in the Actavis docetaxel formulation is acceptable and requires no change to the label.

7 Appendices

7.1 Literature Review/References

Refer to NDA 20449.

7.2 Labeling Recommendations

See final label.

Reference ID: 3244624

It is noted that the applicant correctly removed the pediatric information from label sections 8.4 and 12.3 which are protected by the M-61 / PED exclusivity listed under Taxotere in the Orange Book.

7.3 Advisory Committee Meeting

None

Reference ID: 3244624

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PAUL G KLUETZ
01/14/2013

VIRGINIA E MAHER
01/14/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 203551 **Applicant:** Actavis, Inc. **Stamp Date:** 3/14/2012

Drug Name: Docetaxel Injection Concentrate 20mg/mL **NDA/BLA Type:** 505b2

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?			X	505b2. No Module 5 has been submitted.
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?			X	505b2. No Module 5 has been submitted.
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?			X	505b2. No Module 5 has been submitted.
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			Module 5 is not necessary for this 505b2 application.
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505b2. Reference drug is Docetaxel (Taxotere) NDA 20449
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1			X	505b2. No Module 5 has been submitted.

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

Reference ID: 3123818

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	505b2. No Module 5 has been submitted.
19.	Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Nonclinical data included in this submission has been determined by the respective review teams to be acceptable for filing and review.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The company has taken out the pediatric section from its label. It has submitted a request for pediatric waiver. If drug product is not eligible for a full waiver they request pediatric studies be deferred until after NDA approval.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial			X	There are no covered

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				clinical studies in this submission.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL 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:

This 505b2 application relies on the clinical studies that supported the approval and subsequent indications for Taxotere under the reference listed drug NDA 020449. There are no clinical review issues identifiable for this 505b2 application.

It is noted that the applicant has taken out the pediatric section of the Taxotere label for their proposed label. By doing so they contend that they do not need to adhere to the pediatric exclusivity date. They have also submitted a request for a full pediatric waiver. This will be a review issue.

Paul G. Kluetz, M.D.	4/26/2012
Reviewing Medical Officer	Date
V. Ellen Maher, M.D.	4/26/2012
Clinical Team Leader	Date

Reference ID: 3123818

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PAUL G KLUETZ
04/30/2012

VIRGINIA E MAHER
04/30/2012