CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022312Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22,312**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**July 29, 2009**
PRODUCT:	**Docetaxel Injection**
INTENDED CLINICAL POPULATION:	**Breast Cancer (BC), Non-Small Cell Lung Cancer (NSCLC), Hormone-Refractory Prostate Cancer (HRPC), Gastric Adenocarcionoma (GC), Squamous Cell Carcinoma of the Head and Neck (SCCHN)**
SPONSOR:	**Apotex Inc.**
DOCUMENTS REVIEWED:	**Response to Complete Response Letter**
REVIEW DIVISION:	**Division of Drug Oncology Products**
PHARM/TOX REVIEWER:	**Margaret E. Brower, Ph.D.**
PHARM/TOX SUPERVISOR:	**Haleh Saber, Ph.D.**
DIVISION DIRECTOR:	**Robert Justice, M.D.**
PROJECT MANAGER:	**Christy Cottrell**
Date Entered in DARRTS:	**December 11, 2009**

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Recommend approval.

B. Recommendation for nonclinical studies: The previous need for nonclinical studies for impurity qualification has been resolved.

C. Recommendations on labeling: The content of the pharmacology/toxicology sections of the label are similar to that of the innovator drug label, Taxotere.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
No additional data.

B. Pharmacologic activity
No additional data.

C. Nonclinical safety issues relevant to clinical use
Adverse reactions associated with Docetaxel Injection are expected to be comparable to those reported for Taxotere.

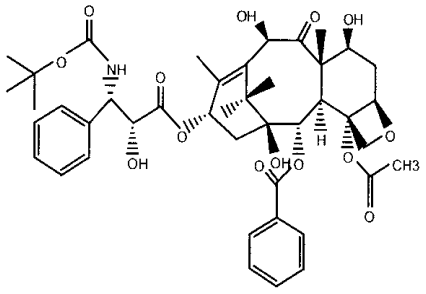
PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: 22,312
Review number: 2
Sequence number/date/type of submission: July 29, 2009/ Response to Complete Response Letter
Information to sponsor: Yes () No (X)
Applicant: Apotex, Inc. Toronto, CA
Manufacturer: (b) (4)

Reviewer name: Margaret Brower, Ph.D.
Division name: Division of Drug Oncology Products
Review completion date: December 10, 2009

Drug:

Trade name: Docetaxel Injection (Reference Listed Drug (RLD): Taxotere)
Generic name: docetaxel
Code name: none
Chemical name: (2R,3S)-N-benzoyl-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5β, 20-Epoxy-1,2α , 4, 7β, 10β , 13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate
Molecular weight/molecular formula: 861.9; $C_{43}H_{53}NO_{14}$
CAS No.: 114977-28-5
Structure:



Relevant INDs/NDAs: NDA 20,449 (RLD), IND 35,555 (RLD), DMF (b) (4)

Pharmacologic class: Microtubule inhibitor

Intended clinical population:

Breast cancer in patients with locally advanced or metastatic cancer following failure of prior chemotherapy. In combination with doxorubicin and cyclophosphamide for adjuvant treatment of patients with node-positive breast cancer.
NSCLC, locally advanced or metastatic, following failure of platinum-based therapy, or in combination with cisplatin in patients who have not previously received chemotherapy.
Prostate cancer in combination with prednisone for treatment of androgen independent (hormone refractory) metastatic cancer
Gastric adenocarcinoma in combination with cisplatin and 5-FU
Head and Neck cancer in combination with cisplatin and 5-FU

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA #22,312 are owned by Apotex or are data for which Apotex has obtained a written right of reference. Any information or data necessary for approval of NDA# 22,312 that Apotex 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 described in the drug's approved labeling. Any data or information described or referenced from a previously approved application that Apotex does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA # 22,312.

INTRODUCTION and DRUG HISTORY:

Taxotere (Docetaxel for Injection Concentrate), NDA 20,449, was approved on May 15, 1996 for the treatment of refractory, locally advanced or metastatic breast cancer. On December 23, 1999, Taxotere was approved as a single agent for the treatment of advanced or metastatic non-small cell lung cancer after failure of platinum containing chemotherapy at the recommended dose of 60-100mg/m^2 administered iv once every three weeks. Taxotere was approved on May 19, 2004 in combination with prednisone for the treatment of androgen independent (hormone refractory) metastatic prostate cancer at a recommended dose of 75mg/m^2 administered once every 3weeks in combination with 5mg oral prednisone BID. In 2005, Taxotere was approved in combination with cisplatin and 5-FU for the treatment of gastric adenocarcinoma. Taxotere (with cisplatin and flurouracil) is also approved for induction treatment of locally advanced SCCHN.

Apotex, Inc. submitted a 505(b)(2) NDA for Docetaxel Injection in 2008. A comparison to the formulation of the reference listed drug (Taxotere) is below.

Clinical formulation: 10mg/mL (same as RLD)
40mg/mL concentrate as 20mg/0.5mL and 80mg/2mL strengths

Qualitative and quantitative compositions of Apotex docetaxel (final dilution for infusion):

Component	Apotex docetaxel (mg/mL)	
	0.3mg/mL minimum	0.74 mg/mL maximum
Docetaxel (anhydrous)	0.3	0.74
Polysorbate 80	(b) (4)	
Ethyl Alcohol (USP)		
Polyethylene glycol 300 NF		
Water for injection USP		
0.9% sodium chloride or 5% dextrose solution		

(b) (4)

The Apotex drug substance (DS) is present as an anhydrous form (injection concentrate), whereas Taxotere, the reference listed drug, uses a trihydrate form of the drug substance.

Apotex added PEG-300 to the docetaxel concentrate (b) (4) in place of polysorbate 80 used in the reference listed drug. Apotex added polysorbate 80 + 95% alcohol USP to the diluent (b) (4) respectively.

The applicant stated that (b) (4) it was not possible to have the same formulation for the diluent as the reference listed drug. The applicant intended to use polysorbate (b) (4)

Alcohol was also used (b) (4)

A Complete Response Letter containing non-clinical deficiencies was sent to the applicant on April 28, 2009. The following paragraph includes the non-clinical deficiencies documented in the Complete Response letter.

Your proposed acceptance criteria for the following impurities (b) (4) (b) (4) in the Docetaxel Injection drug product exceed the ICH Q3B(R2) qualification limit of 0.2%.

Furthermore, you will need to demonstrate that (b) (4) in your drug product both during release, as well as during stability, is below the ICH Q3B(R2) proposed limit of 0.2%.

Impurity specifications that exceed the qualification limit must be lowered to meet the current ICH Q3B(R2) guidance, or the impurities will need to be qualified in nonclinical toxicology studies. Alternatively, justifications for impurity levels may be provided based on appropriate literature citations.

This submission is the applicant's response to these deficiencies.

EXPLANATION OF IMPURITY DEFICIENCIES AND APPLICANT RESPONSE:

The following table includes the specified acceptance criteria submitted by the applicant with the original NDA.

Apotex Drug Product proposed acceptance criteria for individual impurities

Apotex impurity identification	Proposed Acceptance Criteria
(b) (4)	
(b) (4)	

both during release as well as during stability, is below the ICH Q3B(R2) proposed limit of 0.2% (See Complete Response Letter deficiencies above).

Applicant Response to non-clinical deficiencies submitted with Complete Response Letter:

1. (b) (4) have been lowered to the ICH Q3B(R2) qualification limit of NMT 0.2%.
   Agency position: Impurities are within the ICH Q3B(R2) threshold. Non-clinical qualification is not needed.

2. (b) (4) was indicated to be within the ICH Q3B (R2) limit (0.2%) during release, as well as during 18 months of stability.
   Agency position: Impurities are within the ICH Q3B(R2) threshold. Non-clinical qualification is not needed.

3. (b) (4) is considered to be qualified by the applicant based on the presence of the impurity in the reference listed drug.
   Agency position: This impurity is considered qualified since the CMC review team accepted the analytical method used to determine the impurity profile of the 505(b)(2) drug product.

4. (b) (4) is considered qualified by the applicant based on published literature (see below).
   Agency position: This impurity is qualified based on the references submitted and additional references identified in the literature.

Qualification of (b) (4)

(b) (4)

Other issues for approval of NDA 22,312:
In June,2009, Sanofi submitted a Citizen's petition (CP) to the Agency requesting that the Agency require a clinical pharmacokinetic study for proposed new drug products [505(b)(2) or ANDA] containing a ratio of docetaxel: PS80 different from that of Taxotere.

Sanofi claims that docetaxel binds with high affinity to AAG in plasma, and increased concentrations of PS80 may result in increased levels of unbound docetaxel, which may have a greater effect on overall safety (e.g. neutropenia) and pharmacodynamics, than the total docetaxel drug level. As a result, this variability in unbound docetaxel plasma concentration may cause significant differences in the safety and efficacy of the drug product.

After review of data submitted by Sanofi, it was decided by the Center Director that the petitioner did not submit adequate data to justify their position for a 505(b)(2) NDA. At this time there are no data to suggest that the minor change in the docetaxel:PS80 ratio will affect either the safety or the efficacy of Apotex's Docetaxel Injection. The ratio of docetaxel:PS80 is (b) (4) for the 2-vial Taxotere formulation and is (b) (4) for the present 505(b)(2) docetaxel.

Recommendations:
All 505(b)2 impurities documented above with the original Apotex NDA submission have been qualified.

References:

(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22312	ORIG-1		DOCETAXEL INJECTION 40 MG ML

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/s/

MARGARET E BROWER
12/11/2009

HALEH SABER
12/11/2009

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22,312**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**March 27, 2008**
PRODUCT:	**Docetaxel Injection**
INTENDED CLINICAL POPULATION:	**Breast Cancer (BC), Non-Small Cell Lung Cancer (NSCLC), Hormone-Refractory Prostate Cancer (HRPC), Gastric Adenocarcionoma (GC), Squamous Cell Carcinoma of the Head and Neck (SCCHN)**
SPONSOR:	**Apotex Inc.**
DOCUMENTS REVIEWED:	**Module 1, Original submission** **NDA revisions/addendum:** **(July 30, August 20, September 17, December 3, 2008)**
REVIEW DIVISION:	**OODP/DDOP**
PHARM/TOX REVIEWER:	**Margaret E. Brower, Ph.D.**
PHARM/TOX SUPERVISOR:	**Haleh Saber, Ph.D.**
DIVISION DIRECTOR:	**Robert Justice, M.D.**
PROJECT MANAGER:	**Frank H. Cross, Jr.**

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approvable. The sponsor must address the nonclinical issue (see Page 6, External Comment).

B. Recommendation for nonclinical studies: Possible need for nonclinical bridging studies for impurity qualification (see below, section II.A and Page 6, External Comment).

C. Recommendations on labeling: The content of the pharmacology/toxicology sections of the label are similar to that of the innovator drug label for Taxotere. Modifications to these sections were primarily made to comply with conversion to the PLR format.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The proposed acceptance criteria for impurities (b) (4) in the Docetaxel Injection drug product exceed the ICH Q3B(R2) qualification limit of 0.2%. Impurity specifications that exceed the qualification limit must be lowered to meet the current ICH Q3B(R2) guidance, or the impurities will need to be qualified in nonclinical toxicology bridging studies. Alternatively, justifications for impurity levels may be provided based on appropriate literature citations.

The sponsor has interchangeably referred to (b) (4) These degradates are not equal. The sponsor will need to demonstrate that (b) (4) both during release as well as during stability, is below the ICH Q3B(R2) proposed limit of 0.2%. Alternatively, the sponsor may qualify this impurity, or provide justification for the impurity level of (b) (4)

B. Pharmacologic activity

No additional data.

C. Nonclinical safety issues relevant to clinical use

Other than impurity qualification as indicated above, there are no outstanding nonclinical safety issues relevant to clinical use of Docetaxel Injection. Adverse reactions associated with Docetaxel Injection are expected to be comparable to those reported for Taxotere.

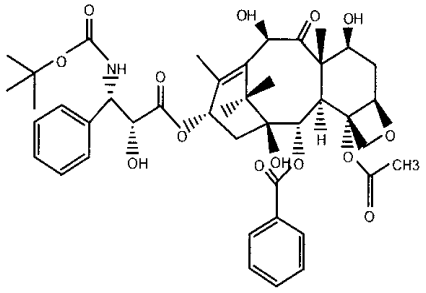
PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: 22,312
Review number: 1
Sequence number/date/type of submission: March 27, 2008/(505(b)(2)/NDA
Information to sponsor: Yes (X) No ()
Sponsor and/or agent: Apotex, Inc. Toronto, CA
Manufacturer: (b) (4)

Reviewer name: Margaret Brower, Ph.D.
Division name: OODP/DDOP
Review completion date: April 14, 2009

Drug:

Trade name: Docetaxel Injection (RLD: Taxotere)
Generic name: docetaxel
Code name: none
Chemical name: (2R,3S)-N-benzoyl-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5β, 20-Epoxy-1,2α , 4, 7β, 10β , 13α-hexahydroxytax-11-en-9-one 4-10-dicetate 2-benzoate
Molecular weight/molecular formula: 861.9; $C_{43}H_{53}NO_{14}$
CAS No.: 114977-28-5
Structure:



Relevant INDs/NDAs: NDA 20,449 (RLD), IND 35,555 (RLD), DMF (b) (4)

Pharmacologic class: Microtubule inhibitor

Intended clinical population:

Breast cancer in patients with locally advanced or metastatic cancer following failure of prior chemotherapy. In combination with doxorubicin and cyclophosphamide for adjuvant treatment of patients with node-positive breast cancer.
NSCLC, locally advanced or metastatic, following failure of platinum-based therapy, or in combination with cisplatin in patients who have not previously received chemotherapy.
Prostate cancer in combination with prednisolone for treatment of androgen independent (hormone refractory) metastatic cancer
Gastric adenocarcinoma in combination with cisplatin and 5-FU
Head and Neck cancer in combination with cisplatin and 5-FU

Clinical formulation: 10mg/mL (same as RLD)
40mg/mL concentrate as 20mg/0.5mL and 80mg/2mL strengths

Qualitative and quantitative compositions of Apotex docetaxel (final dilution for infusion):

Component	Apotex docetaxel (mg/mL)	
	0.3mg/mL minimum	0.74 mg/mL maximum
Docetaxel (anhydrous)	(b) (4)	
Polysorbate 80		
Ethyl Alcohol (USP)		
Polyethylene glycol 300 NF		
Water for injection USP		
0.9% sodium chloride or 5% dextrose solution		

(b) (4)

The Apotex drug substance (DS) is present as an anhydrous form (injection concentrate), whereas Taxotere, the RLD, uses a trihydrate form of the drug substance.

Apotex added PEG-300 to the docetaxel concentrate (b) (4) polysorbate 80 used in the RLD. Apotex added polysorbate 80 + (b) (4) alcohol USP to the diluen (b) (4), respectively.

The sponsor stated tha (b) (4), it was not possible to have the same formulation for the diluent as the RLD. The sponsor intended to use polysorbat (b) (4) Alcohol was also used (b) (4)

Docetaxel Injection concentrate:

Composition	RLD Taxotere	Apotex
Docetaxel (anhydrous)	(b) (4)	
Polysorbate 80		
Polyethylene glycol 300		

*As docetaxel trihydrate in the RLD

Docetaxel diluent:

Composition	RLD Taxotere	Apotex
Alcohol (ethyl alcohol)	(b) (4)	
Polysorbate 80		
Water for injection		

*used as alcohol (b) (4) USP

Route of administration: iv

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA #22,312 are owned by Apotex or are data for which Apotex has obtained a written right of reference. Any information or data necessary for approval of NDA# 22,312 that Apotex 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 described in the drug's approved labeling. Any data or information described or referenced from a previously approved application that Apotex does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA # 22,312.

INTRODUCTION/DRUG HISTORY/IMPURITY CONCERN:

Taxotere (Docetaxel for Injection Concentrate), NDA 20,449, was approved on May 15, 1996 for the treatment of refractory, locally advanced or metastatic breast cancer. On December 23, 1999, Taxotere was approved as a single agent for the treatment of advanced or metastatic non-small cell lung cancer after failure of platinum containing chemotherapy at the recommended dose of 60-100mg/m^2 administered iv once every three weeks. Taxotere was approved on May 19, 2004 in combination with prednisone for the treatment of androgen independent (hormone refractory) metastatic prostate cancer at a recommended dose of 75mg/m^2 administered once every 3weeks in combination with 5mg oral prednisone BID. In 2005, Taxotere was approved in combination with cisplatin and 5-FU for the treatment of gastric adenocarcinoma. Taxotere (with cisplatin and flurouracil) is also approved for induction treatment of locally advanced SCCHN. As mentioned above, the Apotex 505(b)(2) NDA application for Docetaxel Injection is indicated for the same clinical patient population as Taxotere.

Apotex Drug Product proposed acceptance criteria for individual impurities

Apotex impurity identification	Proposed Acceptance Criteria
(b) (4)	

(a) (b) (4) Apotex has been asked to indicate the acceptance criteria for this impurity.

The proposed acceptance criteria for impurities (b) (4) in the Docetaxel Injection drug product exceed the ICH Q3B(R2) qualification limit of 0.2%. Impurity specifications that exceed the qualification limit must be lowered to meet the current ICH Q3B(R2) guidance, or the impurities will need to be qualified in nonclinical toxicology bridging studies. Alternatively, justifications for impurity levels may be provided based on appropriate literature citations.

The proposed Apotex acceptance criteria for (b) (4) at 24 months. (b) (4)

The Apotex acceptance criteria for (b) (4) The sponsor has interchangeably referred to (b) (4). These degradates are not equal. The sponsor will need to demonstrate that (b) (4), both during release as well as during stability, is below the ICH Q3B(R2) proposed limit of 0.2%.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

The proposed acceptance criteria for impurities (b) (4) in the Docetaxel Injection drug product exceed the ICH Q3B(R2) qualification limit of 0.2%. Impurity specifications that exceed the qualification limit must be lowered to meet the current ICH Q3B(R2) guidance, or the impurities will need to be qualified in nonclinical toxicology bridging studies. Alternatively, justifications for impurity levels may be provided based on appropriate literature citations.

In addition, the sponsor has interchangeably referred to (b) (4) (acceptance criteria (b) (4) and (b) (4) These degradates are not equal. The sponsor will need to demonstrate that (b) (4) both during release as well as during stability, is below the ICH Q3B(R2) proposed limit of 0.2%.

Recommendations:
Impurity issues must be resolved as indicated in this review.

External Comment (to sponsor):

Your proposed acceptance criteria for impurities (b) (4) in the Docetaxel Injection drug product exceed the ICH Q3B(R2) qualification limit of 0.2%.

Furthermore, you will need to demonstrate that (b) (4) in your drug product both during release, as well as during stability, is below the ICH Q3B(R2) proposed limit of 0.2%.

Impurity specifications that exceed the qualification limit must be lowered to meet the current ICH Q3B(R2) guidance or the impurities will need to be qualified in nonclinical toxicology studies. Alternatively, justifications for impurity levels may be provided based on appropriate literature citations.

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/s/

Margaret Brower
4/21/2009 03:18:55 PM
PHARMACOLOGIST

Haleh Saber
4/22/2009 09:42:00 AM
PHARMACOLOGIST