

EGPVGT HQT FTW GXCNWCVKQP CPF TGUGCTEJ

Cr r t q x c n R c e n c i g h q t <

APPLICATION NUMBER:

P F C 42/66; 1U/265

Trade Name: Taxotere

Generic Name: docetaxel

Sponsor: Sanofi-Aventis U.S., Inc.

Approval Date: June 3, 2010

Changes: provides for changes to the carton, immediate container, film and diluent labels.

**EGP VGT HQT FTW GXCNWCVKQP CPF
TGUGCTEJ**

APPLICATION NUMBER:
PFC 42/66; IU/265

EQP VGP VU

Tgxlg y u l kphqt o cvkqp kpenwf gf lp vj lu PFC Tgxlg y 0

Cr rt qxcn Ngwgt	Z
Qvj gt Cevkqp Ngwgt u	
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TGO U	
Uwo o ct { Tgxlg y	
Qhleg t kGo r m { gg Nkw	
Qhleg F k gevqt O go q	
Et quu F kær rpg Vgco Ngcf gt Tgxlg y	
O gf lecn Tgxlg y *u+	
Ej go kwt { Tgxlg y *u+	Z
Gpxk qpo gpvcn Cuguo gpv	
Rj cto ceqmi { Tgxlg y *u+	
Uc vkw lecn Tgxlg y *u+	
O let qdkqmi { Tgxlg y *u+	
Er p lecn Rj cto ceqmi { kqrj cto cegw leu Tgxlg y *u+	
Qvj gt Tgxlg y u	Z
Tkum Cuguo gpvcf Tkum O kwi cvkqp Tgxlg y *u+	
Rt qr tlgvt { Pco g Tgxlg y *u+	
Cf o lpkwt cvk g lEqt t gur qpf gpeg F qewo gpv *u+	Z

**EGP VGT HQT FTW GXCNWCVKQP CPF
TGUGCTEJ**

***APPLICATION NUMBER:*
PFC 42/66; IU/265**

CRRTQXCN NGVVGT



NDA 020449/S-043

UWRRNGO GPV CRRTQXCN

sanofi-aventis U.S. LLC
Attention: Gina L. Vestea, PharmD.
Senior Manager, US Regulatory Affairs Marketed Products
Mailstop: 55A-430A
55 Corporate Drive
PO Box 5925
Bridgewater, NJ 08807-5925

Dear Dr. Vestea:

Please refer to your Supplemental New Drug Application (sNDA) dated December 19, 2006, received December 20, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Taxotere (docetaxel) Injection Concentrate, 20 mg and 80 mg.

We acknowledge receipt of your submission dated April 16, 2010.

This “Changes Being Effected 30 Days” supplemental new drug application provides for changes to the carton, immediate container, film and diluent labels.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

Submit final printed carton, immediate container, film and diluent labels that are identical to the enclosed carton, immediate container, film and diluent labels and carton, immediate container, labels submitted on April 16, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)”.

Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**HlpcnRt lqvfg Ectvqp. K o gf kvg Eqpvclpqt. Hko cpf FlwgpvNcdgnlqt Cr rt qxgf PFC24266; IU/2650b**” Approval of this submission by FDA is not required before the labeling is used.

NGVVGTUVQJ GCVNJ ECTG RTQHGUUKQPCNU

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

TGRQTVRPI TGS WKTGO GPVU

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE:

Carton and Container Labeling
Film Labeling
Diluent Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-43	SANOFI AVENTIS US LLC	TAXOTERE

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/s/

AMNA IBRAHIM
06/03/2010
For Dr Robert Justice

**EGP VGT HQT FTW GXCNWCVKQP CPF
TGUGCTEJ**

***APPLICATION NUMBER:*
PFC 42/66; IU/265**

NCDGNPI

FOR FDA SUBMISSION ONLY

Taxotere® (*docetaxel*) NDC 0075-8001-21
Injection Concentrate **20 mg/0.5 mL**
20 mg/0.5 mL docetaxel in polysorbate 80 Before Initial Dilution
Rx ONLY FOR IV INFUSION ONLY AFTER FINAL DILUTION

CAUTION: Withdraw the entire contents of diluent vial (approx. 1.3 mL) to dilute the Taxotere concentrate to achieve a docetaxel concentration of **10 mg/mL** for the initial dilution. Use only the required amount of the initial dilution to prepare the final infusion solution. See package insert for full dilution information.

Store between 2–25°C (36–77°F). Protect from bright light. **2 (FPO) 6**
sagefl-events U.S. LLC, Bridgewater, NJ 08807 5009XXXX 1st 300

Origin United Kingdom ©2010



FOR FDA SUBMISSION ONLY

Each blister pack contains: NDC 0075-8001-20
1 vial NDC 0075-8001-21 **Taxotere**[®] (docetaxel) **20 mg/0.5 mL**
Injection Concentrate Before Initial Dilution
1 vial NDC 0075-8002-21 **Diluent** (13% ethanol in water for injection)

Rx ONLY FOR IV INFUSION ONLY AFTER FINAL DILUTION

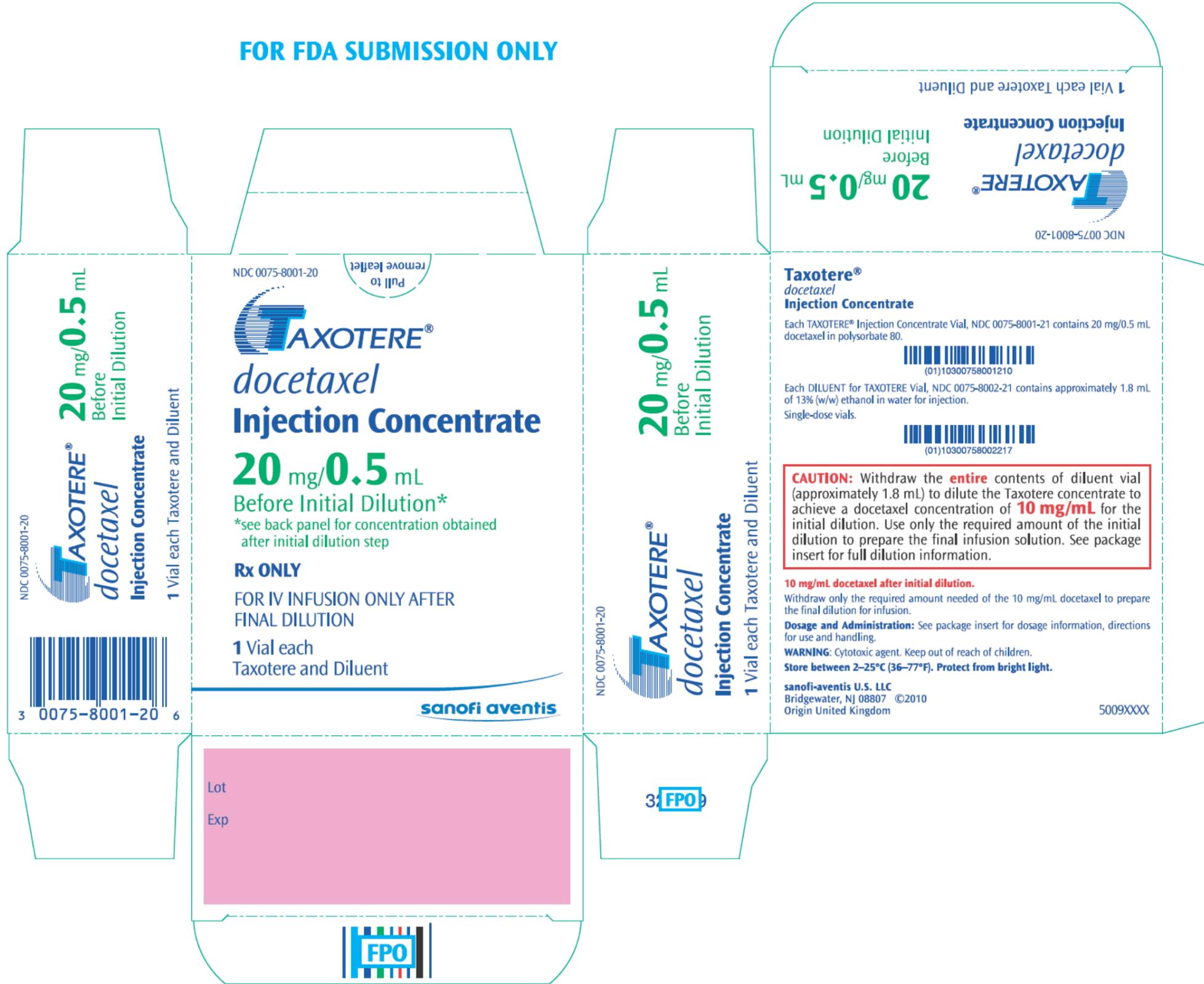
CAUTION: Withdraw the **entire** contents of diluent vial (approx. 1.8 mL) to dilute the Taxotere concentrate to achieve a docetaxel concentration of **10 mg/mL** for the initial dilution. Use only the required amount of the initial dilution to prepare the final infusion solution. See package insert for full dilution information.

Store between 2–25°C (36–77°F). Protect from bright light.
sanofi-aventis U.S. LLC, Bridgewater, NJ 08807 ©2010 5009XXXX
Origin United Kingdom

Lot:

Exp:

FOR FDA SUBMISSION ONLY



NDC 0075-8001-20

TAXOTERE[®]
docetaxel
Injection Concentrate

20 mg/0.5 mL
Before
Initial Dilution

1 Vial each Taxotere and Diluent



3 0075-8001-20 6

NDC 0075-8001-20

Pull to
remove leaflet



docetaxel
Injection Concentrate

20 mg/0.5 mL
Before Initial Dilution*

*see back panel for concentration obtained
after initial dilution step

Rx ONLY

FOR IV INFUSION ONLY AFTER
FINAL DILUTION

1 Vial each
Taxotere and Diluent

sanofi aventis

Lot
Exp



NDC 0075-8001-20

TAXOTERE[®]
docetaxel
Injection Concentrate

20 mg/0.5 mL
Before
Initial Dilution

1 Vial each Taxotere and Diluent

3 FPO

Taxotere[®]
docetaxel
Injection Concentrate

Each TAXOTERE[®] Injection Concentrate Vial, NDC 0075-8001-21 contains 20 mg/0.5 mL docetaxel in polysorbate 80.



(01)10300758001210

Each DILUENT for TAXOTERE Vial, NDC 0075-8002-21 contains approximately 1.8 mL of 13% (w/w) ethanol in water for injection. Single-dose vials.



(01)10300758002217

CAUTION: Withdraw the **entire** contents of diluent vial (approximately 1.8 mL) to dilute the Taxotere concentrate to achieve a docetaxel concentration of **10 mg/mL** for the initial dilution. Use only the required amount of the initial dilution to prepare the final infusion solution. See package insert for full dilution information.

10 mg/mL docetaxel after initial dilution.

Withdraw only the required amount needed of the 10 mg/mL docetaxel to prepare the final dilution for infusion.

Dosage and Administration: See package insert for dosage information, directions for use and handling.

WARNING: Cytotoxic agent. Keep out of reach of children.

Store between 2–25°C (36–77°F). Protect from bright light.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807 ©2010
Origin United Kingdom

5009XXXX

NDC 0075-8001-20
TAXOTERE[®]
docetaxel
Injection Concentrate
20 mg/0.5 mL
Before
Initial Dilution
1 Vial each Taxotere and Diluent

FOR FDA SUBMISSION ONLY

Taxotere[®] (docetaxel) NDC 0075-8001-81
Injection Concentrate **80 mg/2 mL**
Rx ONLY Before Initial Dilution
80 mg/2 mL docetaxel in polysorbate 80
FOR IV INFUSION ONLY AFTER FINAL DILUTION

CAUTION: Withdraw the **entire** contents of diluent vial (approx. 7.1 mL) to dilute the Taxotere concentrate to achieve a docetaxel concentration of **10 mg/mL** for the initial dilution. Use **only** the required amount of the initial dilution to prepare the final infusion solution. See package insert for full dilution information.

Store between 2–25°C (36–77°F). Protect from bright light.
sanofi-aventis U.S. LLC, Bridgewater, NJ 08807
Origin United Kingdom ©2010 5009XXXX

2 of 9909
lot
Exp



FOR FDA SUBMISSION ONLY

Each blister pack contains: NDC 0075-8001-80
1 vial NDC 0075-8001-81 **Taxotere**[®] (*docetaxel*) **80 mg/2 mL**
Injection Concentrate Before
Initial Dilution

1 vial NDC 0075-8002-81 **Diluent** (*13% ethanol in water for injection*)

Rx ONLY FOR IV INFUSION ONLY AFTER FINAL DILUTION

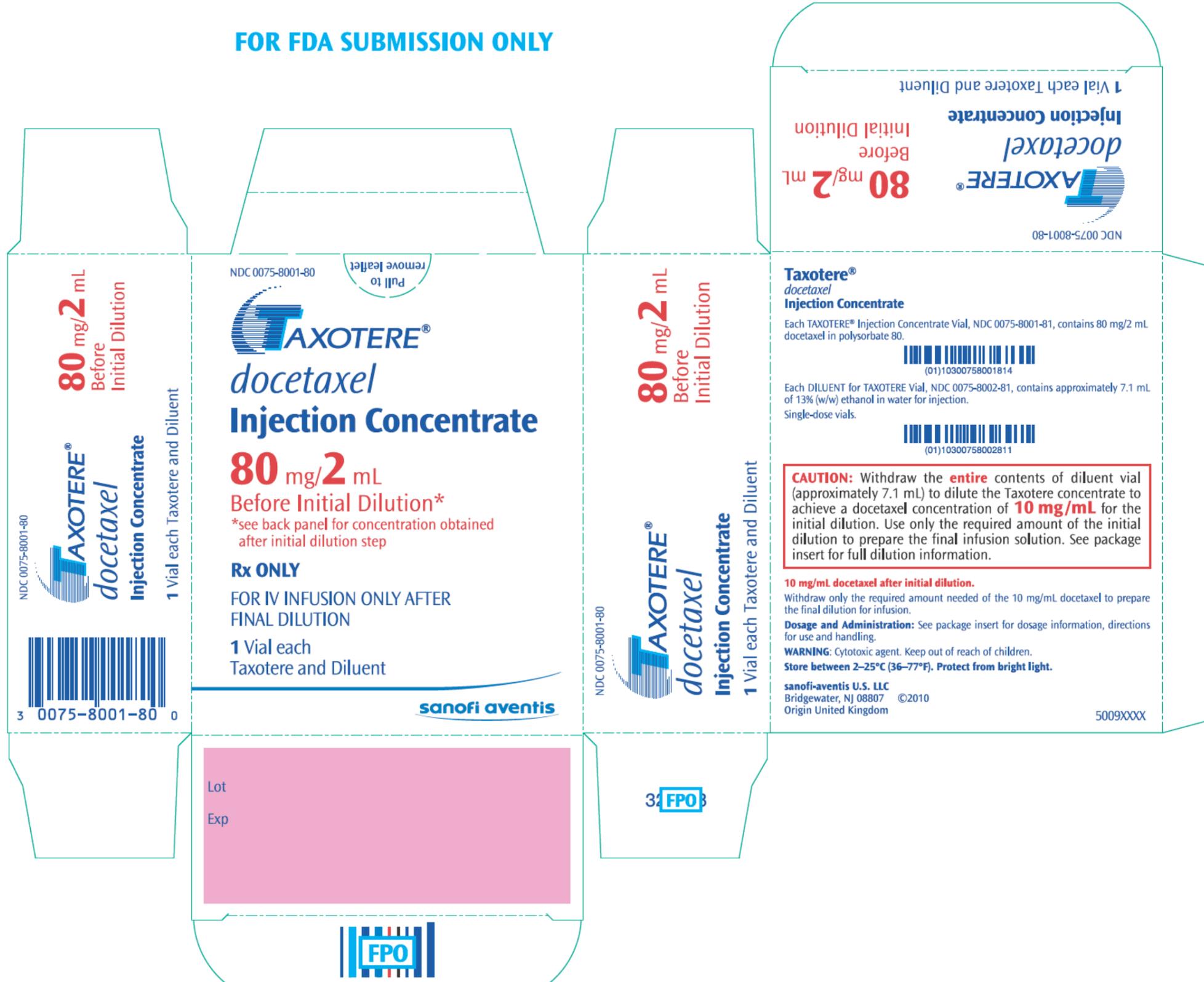
CAUTION: Withdraw the **entire** contents of diluent vial (approx. 7.1 mL) to dilute the Taxotere concentrate to achieve a docetaxel concentration of **10 mg/mL** for the initial dilution. Use only the required amount of the initial dilution to prepare the final infusion solution. See package insert for full dilution information.

Store between 2–25°C (36–77°F). Protect from bright light.
sanofi-aventis U.S. LLC, Bridgewater, NJ 08807 ©2010 5009XXXX
Origin United Kingdom

Lot:

Exp:

FOR FDA SUBMISSION ONLY



NDC 0075-8001-80

TAXOTERE
docetaxel
Injection Concentrate

80 mg/2 mL
Before Initial Dilution

1 Vial each Taxotere and Diluent



3 0075-8001-80 0

NDC 0075-8001-80

Pull to
remove leaflet

TAXOTERE
docetaxel

Injection Concentrate

80 mg/2 mL
Before Initial Dilution*

*see back panel for concentration obtained
after initial dilution step

Rx ONLY

FOR IV INFUSION ONLY AFTER
FINAL DILUTION

1 Vial each
Taxotere and Diluent

sanofi aventis

NDC 0075-8001-80

TAXOTERE
docetaxel
Injection Concentrate

80 mg/2 mL
Before Initial Dilution

1 Vial each Taxotere and Diluent

34 FPO



Lot
Exp

NDC 0075-8001-80

TAXOTERE
docetaxel
Injection Concentrate

80 mg/2 mL
Before Initial Dilution

1 Vial each Taxotere and Diluent

Taxotere
docetaxel
Injection Concentrate

Each TAXOTERE[®] Injection Concentrate Vial, NDC 0075-8001-81, contains 80 mg/2 mL docetaxel in polysorbate 80.



(01)10300758001814

Each DILUENT for TAXOTERE Vial, NDC 0075-8002-81, contains approximately 7.1 mL of 13% (w/w) ethanol in water for injection. Single-dose vials.



(01)10300758002811

CAUTION: Withdraw the **entire** contents of diluent vial (approximately 7.1 mL) to dilute the Taxotere concentrate to achieve a docetaxel concentration of **10 mg/mL** for the initial dilution. Use only the required amount of the initial dilution to prepare the final infusion solution. See package insert for full dilution information.

10 mg/mL docetaxel after initial dilution.

Withdraw only the required amount needed of the 10 mg/mL docetaxel to prepare the final dilution for infusion.

Dosage and Administration: See package insert for dosage information, directions for use and handling.

WARNING: Cytotoxic agent. Keep out of reach of children.

Store between 2–25°C (36–77°F). Protect from bright light.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807 ©2010
Origin United Kingdom

5009XXXX

FOR FDA SUBMISSION ONLY

DILUENT NDC 0075-8002-81
13% ethanol in water for injection **Rx ONLY**
for **Taxotere® (docetaxel) 80 mg**
Injection Concentrate

CAUTION: Use the **entire** contents of this vial (approx. **7.1 mL**) to dilute the contents of Taxotere 80 mg vial. See package insert for full dilution information. **Store between 2–25°C (36–77°F). Protect from bright light.**

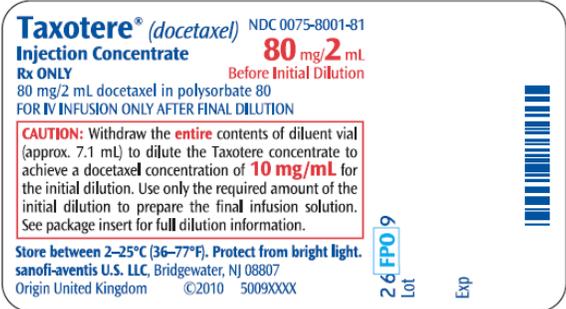
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807 ©2010
Origin United Kingdom 5009XXXX Lot Exp



**EGP VGT HQT FTW GXCNWCVKQP CPF
TGUGCTEJ**

***APPLICATION NUMBER:*
PFC 42/66; IU/265**

EJ GO KVTI TGXKGY *U+

CHEMIST'S REVIEW		1. ORGANIZATION ONDQA		2. NDA NUMBER 20-449	
3. NAME AND ADDRESS OF APPLICANT (City and State) Sanofi-Aventis U. S. LLC 200 Crossing Boulevard Bridgewater, NJ 08807				4. AF NUMBER	
6. NAME OF DRUG Taxotere Injection Concentrate				7. NONPROPRIETARY NAME Docetaxel	
				5. SUPPLEMENT (S) NUMBER(S) DATES(S) SLR 043 Amendment 12-19-2006 04-16-2010	
8. SUPPLEMENT PROVIDES FOR: DP bottle and carton label revision.				9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Antineoplastic		11. HOW DISPENSED RX <input checked="" type="checkbox"/> OTC		12. RELATED IND/NDA/DMF None	
13. DOSAGE FORM(S) Injection		14. POTENCY 20 mg and 80 mg/vial			
15. CHEMICAL NAME AND STRUCTURE (2R,3S)-N-Carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5β,20-epoxy-1,2α,4α,7β,10β,8,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Molecular formula: C ₄₃ H ₅₃ NO ₁₄ · 3H ₂ O. Molecular weight: 861.93				16. RECORDS AND REPORTS CURRENT YES <input checked="" type="checkbox"/> NO REVIEWED YES <input checked="" type="checkbox"/> NO	
17. COMMENTS The original supplement 43 was submitted on 12/19/2006 and has been reviewed by DMEPA with several comments. The additional comment was forwarded to company on 4-13-2010. The response to DMEPA's comments was submitted on 4-16-2010 to accept all from DMEPA in revision of drug carton and vial label (adding "Caution" to avoid the confusion with one vial DP in supplement 54):					
					
DMEPA completed the second review and found all revised labeling to be acceptable dated 4-20-2010.					
There are no concerns from the CMC standpoint.					
18. CONCLUSIONS AND RECOMMENDATIONS Approval is recommended based on DMEPA's comments.					
19. REVIEWER					
NAME Chengyi Liang, Ph.D.		SIGNATURE		DATE COMPLETED 4-21-2010	
DISTRIBUTION	ORIGINAL JACKET	DIVISION FILE	Reviewer: C.Liang	CSO:	Branch Chief H. Patel

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-43	SANOFI AVENTIS US LLC	TAXOTERE

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/s/

CHENG YI LIANG
04/21/2010

HASMUKH B PATEL
04/22/2010

**EGP VGT HQT FTW GXCNWCVKQP CPF
TGUGCTEJ**

***APPLICATION NUMBER:*
PFC 42/66; IU/265**

QVJ GT TGXKGY *U+



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: January 16, 2009

To: Robert Justice, MD, Director
Division of Drug Oncology Products

Thru: Kristina C. Arnwine, PharmD, Team Leader
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Recommendations

Drug Name: Taxotere (Docetaxel) Injection Concentrate
20 mg/0.5 mL and 80 mg/2 mL
(40 mg/mL)

Application Type/Number: NDA 20-449 (SLR-043)

Applicant: Sanofi-aventis U.S. LLC

OSE RCM #: 2009-118

EXECUTIVE SUMMARY

1 INTRODUCTION

This memorandum is written in response to a follow-up meeting with the Division of Drug Oncology Products on Taxotere (Docetaxel) Injection Concentrate, NDA 20-449. The Applicant submitted a CBE supplement on December 19, 2006. The Division has not yet taken an action on this supplement so they requested comments from DMEPA on the labels and labeling that were submitted. Please note that DMEPA initially reviewed this supplement in OSE Review 2007-548, dated July 9, 2007.

2 MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis reviewed the following labels and labeling submitted by the Applicant on December 19, 2006.

- **Container Labels:** 20 mg/0.5 mL and 80 mg/2 mL
- **Carton Labeling:** 20 mg/0.5 mL and 80 mg/2 mL
- **Diluent Label:** For Taxotere 20 mg

Additionally, the following label and labeling (obtained from the Annual Report for Taxotere Injection Concentrate submitted on July 10, 2008 which covers the period May 4, 2007 through May 13, 2008) were reviewed.

- **Diluent Label:** For Taxotere 80 mg
- **Film Labeling:** 20 mg/0.5 mL and 80 mg/2 mL

3 DISCUSSION

In response to the Division's current request and in effort to provide updated comments, DMEPA has re-evaluated all of the container labels and carton labeling for Taxotere to help ensure that revisions are consistent throughout the product line of Docetaxel.

DMEPA evaluated the labels and labeling and wanted the resultant concentration increased in size and prominence because there were still complaints concerning the inability to read and locate this information on the container and carton labeling. We also made other minor edits. We discussed our proposed revisions with the Division and they concurred with our recommendations. Additionally, CMC stated there were discrepancies between the container/carton labeling and the insert labeling [REDACTED] (b) (4) [REDACTED]. We acknowledged we would support their recommendations for revising the labels and labeling to make these statements consistent.

4 RECOMMENDATIONS

In addition to the recommendations made in OSE Review 04-0208, which the Applicant has already implemented, we have the following recommendations for revisions to the labels and labeling:

A. Container Labels

For the caution statement, increase the prominence of the drug concentration obtained after the initial dilution (10 mg/mL) by boxing the entire caution statement and increasing the font size of “10 mg/mL”.

B. Carton Labeling

1. For the caution statement, increase the overall size of the caution statement and increase the prominence of the drug concentration obtained after the initial dilution (10 mg/mL) by boxing the entire caution statement and increasing the font size of “10 mg/mL”.
2. Change the statement “**see back panel for initial concentration*” to read “**see back panel for concentration obtained after initial dilution step*”.

C. Diluent Label for Taxotere 80 mg

1. [REDACTED] (b) (4)
2. For the caution statement, highlight the bolded statements “Caution” and “entire” in a contrasting color [REDACTED] (b) (4)

D. Film Labeling

1. For the caution statement, highlight the bolded statements “Caution”, “entire”, and “10 mg/mL” in a contrasting color as you have already done to the caution statement on the container and carton labeling.
2. For the caution statement, [REDACTED] (b) (4) increase the prominence of the drug concentration obtained after the initial dilution (10 mg/mL) by boxing the entire caution statement and increasing the font size of “10 mg/mL”.

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this page is the manifestation of the electronic signature.**

/s/

Loretta Holmes
1/16/2009 04:37:30 PM
DRUG SAFETY OFFICE REVIEWER

Kristina Arnwine
1/16/2009 04:48:49 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
1/16/2009 04:52:16 PM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: May 12, 2010

To: Robert Justice, MD, Director
Division of Drug Oncology Products

Thru: Kristina C. Arnwine, PharmD, Team Leader
Division of Medication Error Prevention and Analysis

From: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Taxotere (Docetaxel) Injection Concentrate
20 mg/0.5 mL and 80 mg/2 mL
(40 mg/mL)

Application Type/Number: NDA 20-449 (SLR-043)

Applicant: Sanofi-aventis U.S. LLC

OSE RCM #: 2009-118

1 INTRODUCTION

This memorandum is written in response to a request from the Division of Drug Oncology Products for assessment of the Applicant's April 16, 2010 revisions to the container labels, diluent labels, film (blister) and carton labeling for Taxotere Injection to identify areas that could contribute to medication errors. These revisions were made in response to the Agency's label and labeling recommendations identified in OSE Labeling Review #2009-118, dated January 16, 2009.

2 MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis reviewed the following revised labels and labeling submitted by the Applicant on April 16, 2010 (see Appendix A).

- **Container Labels:** 20 mg/0.5 mL and 80 mg/2 mL
- **Carton Labeling:** 20 mg/0.5 mL and 80 mg/2 mL
- **Diluent Label:** For Taxotere 20 mg
- **Diluent Label:** For Taxotere 80 mg
- **Film (Blister) Labeling:** 20 mg/0.5 mL and 80 mg/2 mL

3 DISCUSSION

Review of the revised documents show that the Applicant implemented DMEPA's recommendations under OSE Review 2009-118.

4 CONCLUSION AND RECOMMENDATIONS

The revised labels and labeling submitted by the Applicant adequately address our concerns from a medication error perspective.

If you have further questions or need clarifications, please OSE Project Manager Sarah Simon at 301-796-5205.

2 Pages Immediately Following Withheld - b(4) Draft Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-43	SANOFI AVENTIS US LLC	TAXOTERE

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/s/

LORETTA HOLMES
05/12/2010

KRISTINA C ARNWINE
05/12/2010

MEMORANDUM

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; WO22, Mail Stop 4447
Center for Drug Evaluation and Research

To: Robert Justice, MD
Director, Division of Drug Oncology Products
HFD-150

Through: Linda Y. Kim-Jung, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Loretta Holmes, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: March 23, 2007

Subject: **DMETS Label and Labeling Review**
Drug: Taxotere (Docetaxel) Injection Concentrate; 20 mg/0.5 mL and 80 mg/2 mL
NDA#: 20-449 (SLR-043)
Sponsor: Sanofi-aventis U.S. LLC

Review #: 2007-548

I. INTRODUCTION

This review is in response to a request from the Division of Drug Oncology Products for a review of Supplement 043 which provides for the revised container labels and carton labeling for the 20 mg/0.5 mL and 80 mg/2 mL vial strengths of Taxotere Injection Concentrate and the revised container label for the diluent vial used for the 20 mg active vial.

This supplement is in response to OSE Review 04-0208 (dated February 6, 2006) which provided recommendations to minimize medication errors due to confusing labels and labeling of Taxotere Injection Concentrate.

II. ADVERSE EVENT REPORTING SYSTEM (AERS) AND DRUG QUALITY REPORTING SYSTEM (DQRS) SEARCHES

A search of the *Adverse Event Reporting System* (AERS) and the *Drug Quality Reporting System* (DQRS) was conducted on March 22, 2007 for medication error reports concerning Taxotere from the time of our last search (November 7, 2005; summarized in OSE Review 04-0208) until March 22, 2007. AERS was searched for all foreign and domestic cases using the MedDRA high level group term "medication errors". The drug names were searched using the terms "Taxotere", "Taxot%", "Docetaxel", and "Docetax%".¹ Additionally, the DQRS was searched for all medication error reports concerning Taxotere during this same time period.

DMETS retrieved three additional cases (n=3) from AERS and DQRS searches. However, one case was a duplicate, thus, two additional cases were received in this time frame. Both of the relevant cases were domestic reports received by the Agency in 2006. The narratives of these two cases follow.

¹ Wildcard (%) used to account for all spellings, correct and incorrect, of Taxotere and Docetaxel.

Case 1: The reporter complains that the labeling on the peel off cover of the blister pack is misleading because the 80 mg/2 mL type is bold and in red, while the final concentration of 10 mg/mL is also bold but is in a smaller font size and could be easily missed since it is not in red. The reporter also complains that the terminology referring to “initial dilution” could be misinterpreted to mean the undiluted concentration of 80 mg/mL which would result in underdosing the patient.

Case 2: The reporter complains that the front of the box of Taxotere is labeled prominently with the concentration of 80 mg/2 mL. However, the final concentration of 10 mg/mL after dilution is in bold print on the back of the box, but it is in smaller print and much less prominent than the 80 mg/2 mL concentration displayed on the front and sides of the carton and with no mention of the need for further dilution on the front of the box, there is the potential for dose calculation errors. The reporter continues and states that this resulted in a near miss in which a pharmacy technician calculated the amount of Taxotere solution needed using the 80 mg/2 mL concentration. The error was caught by the pharmacist.

III. LABEL AND LABELING RECOMMENDATIONS

DMETS acknowledges that the sponsor has addressed most of our recommendations as presented in OSE Review 04-0208. Additionally, DMETS believes that the colors used in the revised labels and labeling will address the issue of the lack of prominence of the “10 mg/mL” statement on the container labels and carton labeling as cited in one of the above medication error reports. However, the size of this statement is inadequate and needs to be increased or relocated altogether. We have the following recommendations to further minimize user error and maximize patient safety.

A. GENERAL COMMENTS

1. [REDACTED] (b) (4)
2. [REDACTED] (b) (4)
3. Increase the size of the resultant concentration (10 mg/mL) [REDACTED] (b) (4)
4. Box the caution statement or, alternatively, box the “10 mg/mL” information that is located within the caution statement.

B. CONTAINER LABELS (Active vial)

See General Comments.

C. CONTAINER LABEL (Diluent)

DMETS has no comments at this time.

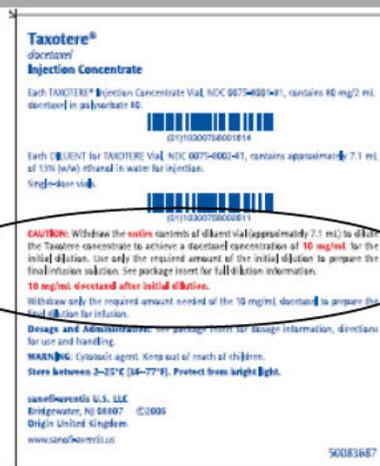
D. CARTON LABELING

1. See General Comments.
2. [REDACTED] (b) (4)

3. Increase the overall font size of the important caution statement located on the back panel in order to increase its prominence and readability (b) (4)



1. Increase the font size of the caution statement.
2. Box the caution statement or, alternatively, box the "10 mg/mL" information that is located within the caution statement.



E. BLISTER PACK LABELING

1. See General Comments.
2. In the caution statement, highlight the following words in bold red type: "Caution", "entire", and "10 mg/mL", similar to the container labels. If space allows, increase the overall font size of the caution statement in order to increase its prominence and readability.

1. Highlight the following words, located in the caution statement, with bold red type :
 “Caution”, “entire”, and “10 mg/mL” in order to make the statement and the selected words more prominent. If space allows, increase the overall font size of the caution statement.
2. Box the caution statement.



F. PACKAGE INSERT LABELING

PREPARATION AND ADMINISTRATION SECTION

See Comment A-2. Revise the wording in this section accordingly.

Additionally, DMETS met with the post-marketing chemistry review team for Taxotere on June 12, 2007. The chemistry team (b) (4)



In summary, DMETS recommends implementation of the label and labeling recommendations outlined above. Please copy DMETS on any correspondence to the sponsor pertaining to this review. If you have questions or need clarification, please contact Samuel Chan, OSE Project Manager, at 301-796-2283.

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

/s/

Loretta Holmes
7/9/2007 02:49:55 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
7/9/2007 04:05:41 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/10/2007 04:15:01 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/10/2007 04:40:44 PM
DRUG SAFETY OFFICE REVIEWER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20-449/S-043

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

From: Fagbami, Modupe
Sent: Tuesday, April 13, 2010 3:07 PM
To: 'Gina.Vestea@sanofi-aventis.com'
Subject: NDA 20449-S-043 OSE Recommendations
Importance: High

Hi Gina,

Please find the following recommendations for your NDA 020449 S-043 for your response on or before 12 :00 noon EST, Friday, April 15, 2010.

They are:

A. Container Labels

For the caution statement, increase the prominence of the drug concentration obtained after the initial dilution (10 mg/mL) by boxing the entire caution statement and increasing the font size of "10 mg/mL".

B. Carton Labeling

1. For the caution statement, increase the overall size of the caution statement and increase the prominence of the drug concentration obtained after the initial dilution (10 mg/mL) by boxing the entire caution statement and increasing the font size of "10 mg/mL".

2. Change the statement "***see back panel for initial concentration***" to read "***see back panel for concentration obtained after initial dilution step***".

C. Diluent Label for Taxotere 80 mg

(b) (4)



2. For the caution statement, highlight the bolded statements "Caution" and "entire" in a

contrasting color

(b) (4)

D. Film Labeling

1. For the caution statement, highlight the bolded statements “Caution”, “entire”, and “10 mg/mL” in a contrasting color as you have already done to the caution statement on the container and carton labeling.

2. For the caution statement, increase the overall size of the caution statement and increase the prominence of the drug concentration obtained after the initial dilution (10 mg/mL) by boxing the entire caution statement and increasing the font size of “10 mg/mL”.

Please let me know if you have any questions.

Thank you.

Modupe O. Fagbami

RPM

Division of Drug Oncology Products

Office of Oncology Drug Products

CDER, FDA

10903 New Hampshire Avenue

WO-22, Room 2108

Silver Spring, Maryland 20993

Phone: 301-796-1348

Fax: 301-796-9845

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20449	SUPPL-43	SANOFI AVENTIS US LLC	TAXOTERE

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

/s/

MODUPE O FAGBAMI
04/13/2010

REQUEST FOR CONSULTATION

TO (Division/Office): **OSE, Samuel Chan**

FROM:
Frank Cross, PM, 301-796-0876

DATE 2/6/07	IND NO.	NDA NO. 20-449	TYPE OF DOCUMENT SLR-043	DATE OF DOCUMENT 12/19/06
----------------	---------	-------------------	-----------------------------	------------------------------

NAME OF DRUG TAXOTERE® (docetaxel) Injection Concentrate, 20 mg and 80mg	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 5/20/07
--	------------------------	------------------------	------------------------------------

NAME OF FIRM: **Sanofi-aventis U.S. Inc.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): New NDA |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
-------------------------------	--------------------------------

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: **For this new sNDA, please provide a DMETS review. This supplement was submitted in response to comments previously conveyed from DMETS (see attached DMETS review from DFS). Per the cover letter of the applicant's cover letter (EDR: [\CDSESUB1\N20449\S_043\2006-12-19](#)):**

Reference is made to NDA 20-449 for TAXOTERE® (docetaxel) Injection Concentrate. Reference is also made to supplemental drug application S-034, which was approved on November 5, 2005. This supplement provided for changes to the TAXOTERE® carton, blister, active vial, and diluent vial labels. Finally reference is made to an email correspondence between Ms. Ann Staten (FDA) and Mark Moyer (sanofi-aventis) on February 24, 2006, which provided additional carton/labeling revisions at the request of the Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety.

Thanks, Frank

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

- MAIL HAND DFS

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

MEMORANDUM	Division of Medication Errors and Technical Support (DMETS) Office of Drug Safety HFD-420; White Oak 22, Mail Stop 4447 Center for Drug Evaluation and Research
-------------------	--

DATE OF REVIEW: December 29, 2005

TO: Robert Justice, M.D.
Director, Division of Drug Oncology, HFD-106

FROM: Kimberly Pedersen, RPh
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

THROUGH: Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

CC: Ann Staten
Project Manager, Division of Oncology Drug Products, HFD-106

SUBJECT: **DMETS MEDICATION ERRORS POSTMARKETING SAFETY REVIEW**
Drug: Taxotere (Docetaxel) Injection Concentrate
NDA# 20-449
Sponsor: Aventis Pharmaceuticals

PROJECT #: 04-0208

I. EXECUTIVE SUMMARY

In May 1999 (ODS consult # 99-0012), DMETS reviewed fourteen cases of medication errors involving the “drug maladministration” of Taxotere. Of these fourteen cases, nine involved issues with labeling and six involved confusion due to the expression of strength. DMETS later reviewed the revised labels and labeling (July 2001, ODS consult # 99-0012-2) and again in September 2002. In all circumstances, DMETS made recommendations for labeling changes.

DMETS conducted a recent search of the FDA Adverse Event Reporting System (AERS) and Drug Quality Reporting System (DQRS) for recent cases of confusion involving Taxotere. In total, DMETS has identified fifty-one cases (thirty-six from AERS and fourteen from DQRS). The following issues emerged upon review of these cases: name confusion between Taxol and Taxotere, wrong route of administration, missing scheduled dosing, confusion with what type of bag results in Taxotere stability, inadequate labeling in regard to refrigeration, confusion with proper identification of the diluent compared to active drug, and confusion with vial content and concentration (before and after dilution).

DMETS found that most of these issues have been addressed by previous label and labeling changes *except* for the confusion between Taxotere and Taxol and confusion over the total drug content and concentration. To address these remaining issues, DMETS recommends implementation of the label and labeling revisions outlined in Section IV of this review.

II. BACKGROUND

On May 14, 1996, Rhone-Poulenc Rorer Pharmaceuticals received approval for Taxotere (Docetaxel) Injection Concentrate. At this time, Taxotere is owned by Aventis Pharms (culmination of the merger of Hoechst and Rhone) and indicated for the treatment of locally advanced or metastatic breast cancer in patients after failure to prior chemotherapy, as a single agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy, and in combination with prednisone for the treatment of patients with androgen independent metastatic prostate cancer.

DMETS has reviewed Taxotere from a post-marketing perspective twice in the past. In May 1999 (ODS consult # 99-0012), fourteen cases were found under “drug maladministration.” Of these, nine involved issues associated with labeling and six were reviewed for confusion due to the expression of strength. DMETS later reviewed the revised labels and labeling (July 2001, ODS consult # 99-0012-2). DMETS again reviewed the revised labels and labeling for Taxotere in September 2002. In all circumstances, DMETS made recommendations for labeling changes.

III. RISK ASSESSMENT

A. AERS and DQRS SEARCHES

Searches were conducted on November 7, 2005 using the FDA Drug Quality Reporting System (DQRS) and on December 20, 2005 using the FDA Adverse Event Reporting System (AERS). AERS was searched for all foreign and domestic cases using the MedDRA high level group term of “medication errors.” The drug names searched were “Taxot%¹ and “Docetax%” with eighty-seven (n=87) reports found.

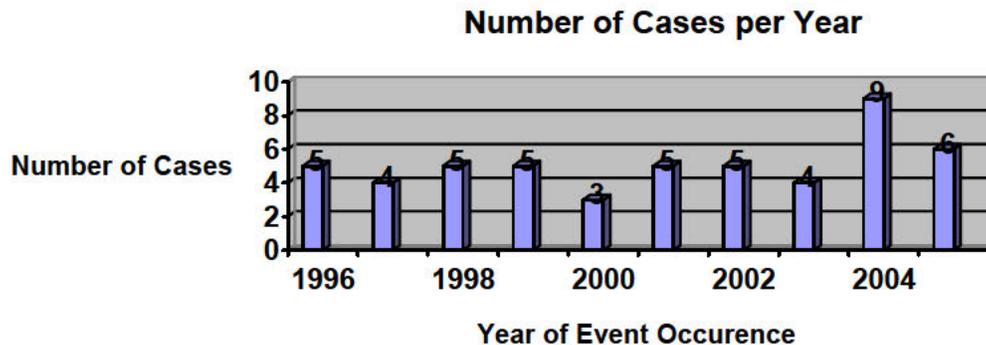
Of the eighty-seven reports found in the AERS search, fifty were excluded from this analysis due to a lack of relevance with DMETS purport. The reports involved adverse events involving Taxotere (medication errors with other medications or clinical circumstance), overdose or lack of compliance with other medications, non-compliance with study protocols, drug exposure in pregnancy, intentional overdose, missed doses (resulting from adverse events), and duplicate cases. The remaining thirty-seven cases will be reviewed with the DQRS cases discovered. Forty-one reports were found in the DQRS search. Fourteen cases were included in this review, as the remaining reports (n=27) were duplicates (of other DQRS or AERS reports) or related only to quality control issues.

¹ Wildcard (%) used to account for all spellings, correct and incorrect, of Taxotere and Docetaxel.

Thus, DMETS will review fifty-one cases in the following analysis (see Appendix 1 for the complete report listing).

B. Identification of the Causes of Error

Analysis of the fifty-one cases uncovered the following types of medication error: wrong route of administration, missing scheduled dosing, confusion over type of IV bag (i.e. bag composition) used for mixing, confusion over labeled refrigeration statement, confusion with proper identification of the diluent compared to active drug, confusion between Taxol and Taxotere, and confusion with vial content and concentration (before and after dilution). The chart below represents the date of occurrence of these errors.



1. Wrong Route of Administration Errors and Scheduled Dosing Errors (n=6)

Six cases relating to wrong route of administration or errors in scheduled dosing were reported to FDA. These errors appear to be due to performance and poor technique and not the result of confusion or insufficient labeling. The same is true of the scheduled dosing errors that appear to be due to clinical confusion or lack of documentation, and not resulting from poor label or labeling design. Thus, DMETS does not believe there are any regulatory or labeling methods FDA can implement that will prevent these types of error. Prevention will need to focus on education on the proper administration technique.

2. Storage (n=1)

There was one case (2002) that implicated confusion with the refrigeration of Taxotere due to possible misleading labeling. The reporter described a reference in the preparation and administration section of the package insert that noted the drug product being stored under refrigeration with the storage temperatures of 2 to 25 degrees Celsius. However, DMETS found that the most recent labeling status does not reflect any storage discrepancy as there was no mention of “refrigeration” and only a reference to the storage temperature range. Thus, DMETS has no recommendations for additional labeling changes.

3. Type of Infusion Bag (n=2)

Two cases (1998 and 2001) described a reference to Taxotere being prepared in bottles or plastic bags of polypropylene or polyolefin, which was placed at the end of the preparation and administration section. However, we note this information has been relocated to the fourth paragraph of this section, making it easily accessible to practitioners. Thus, DMETS has no further recommendations for labeling changes in reference to this problem.

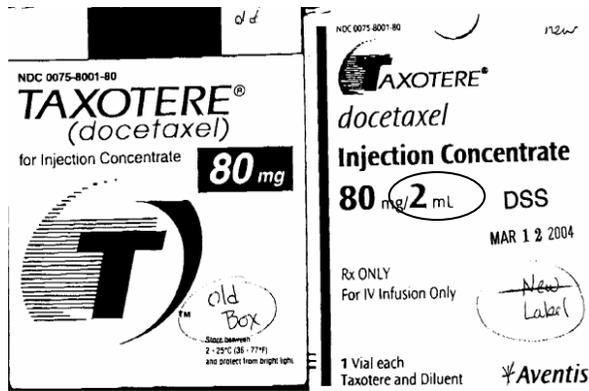
4. Confusion over Diluent Label (n=2)

Confusion with the proper identification of the diluent was addressed in two cases (1996 and 1999). The reporters were concerned that the diluent could be confused with active drug product. However, a search of the agency databases found no reports of the actual administration of incorrect product. Another case (2002) describes a lack of identification of the volume of the diluent on the label. Labeling changes have improved the appearance of the label. Specifically with respect to the prominence of the “Taxotere” reference in addition to noting the volume in the caution statement on the label. However, DMETS has suggestions to improve the diluent container label later in this review (see Section IV).

5. Confusion with Taxotere vial content and concentration (before and after dilution) (n=33, one from a foreign source)

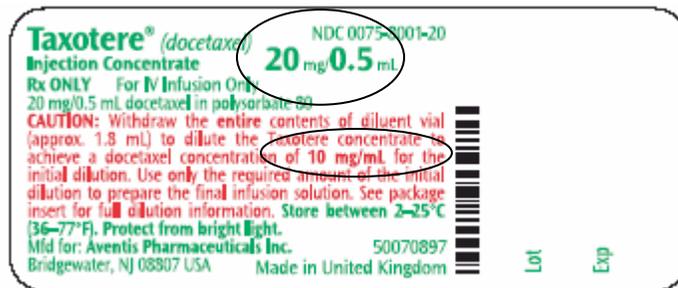
Thirty-three cases involve some type of confusion with Taxotere labels and/or labeling. The majority of the cases are complaints of confusion between the strength and concentration of Taxotere, before and after dilution. Most cases did not refer to actual errors or patient involvement in the preparation of Taxotere, but addressed comprehension issues or confusion. One case from a foreign source was poorly documented to the cause of the *overdose* (identified confusion have resulted in underdosing); thus, will not be reviewed further.

From November 2003 to September 2005, there were fifteen cases describing confusion with Taxotere labels or labeling. Of these, four involved a patient receiving the incorrect dose (two under dosed and one unknown) or confusion over the correct preparation of Taxotere (under dosing). The remaining cases address concern with the new label presentation and the increased potential for confusion and error. Shown on page 5 are the changes made to the product label at that time, which include the addition of the active drug milliliter content (prior to dilution).



In each of these cases, the same root causes were identified that include the addition of the milliliter content of the active drug prior to dilution on the front panel (0.5 mL for the 20 mg and 2 mL for the 80 mg) and the lack of adequate prominence of the final concentration of 10 mg/mL, as it is merely noted on the back panel.

In addition, one reporter noted the actual container label prominently noted the 80 mg/2 mL content instead of the final concentration of 10 mg/mL, which led to confusion and underdosing (see below).



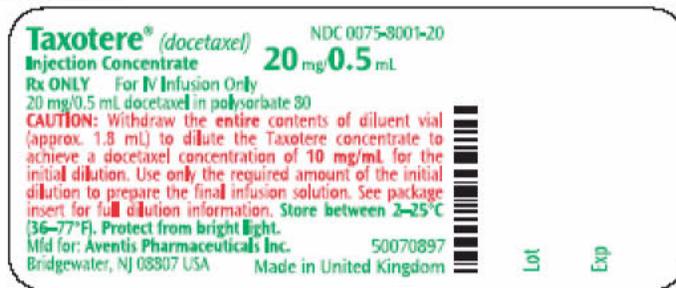
There has been an additional update to the labeling (letter dated May 11, 2005) since the last update in 2003 to help alleviate confusion and medication error. The changes shown on page 6 include the addition of the statement “before initial dilution” and “after final dilution”:

Previous:

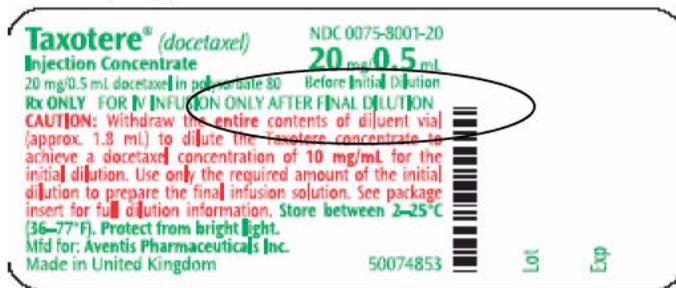
Newly Approved:



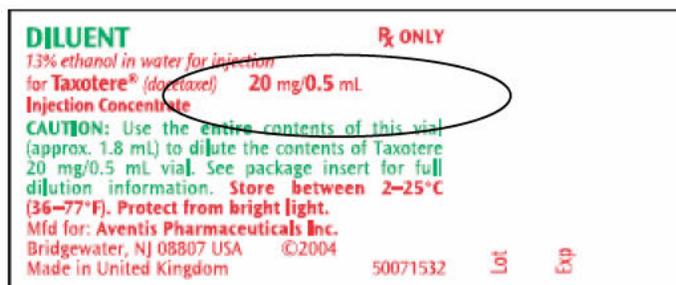
Previous:



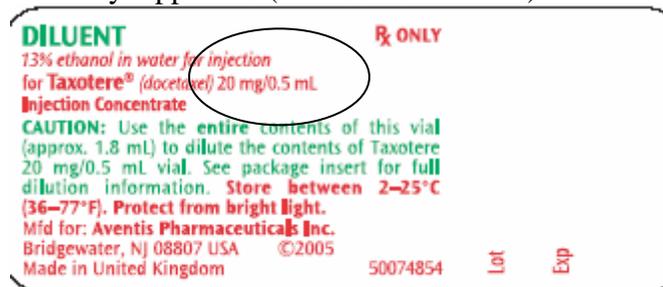
Recently Approved:



Previous:



Recently Approved (with decreased font):



As this was a recent update, DMETS will continue to monitor for confusion or if medication error occur because of this new labeling. Additionally, we have suggestions for further revisions that will help lead the practitioner to the important information on the label (see section IV of this review).

To explain why DMETS believes further revisions are necessary at this time, an analysis of historical data is provided. This helps to elucidate the levels of confusion that occurred with each of the label updates.

There were eighteen cases of confusion with Taxotere dosing from August 1996 to May 2002. Of these cases, four noted actual confusion in preparation or infusion of the incorrect dose. The remaining cases addressed confusion with the concentration and total vial content without specific reference to an error occurring. The three primary issues were confusion with the actual amount of diluent, confusion with the total vial content, and concern with the lack of significant documentation of the final concentration (10 mg/mL).

- Diluent Amount Confusion

For the cases of confusion with the diluent (n=10), the labels and labeling documented a fill volume of 1.74 mL and 7.33 mL, for the 20 mg and 80 mg respectively. Many practitioners described that they were unable to extract this the total fill volume from the vial leading to questioning of the final concentration.

- Total Vial Content

The second point of confusion involved the total vial content (n= 5), which was documented as both 23.6 mg/0.59 mL and 94.4 mg/2.36 mL and 20 mg/0.5 mL and 80 mg/2 mL, which in turn led to confusion over the actual content and concentration (see below).

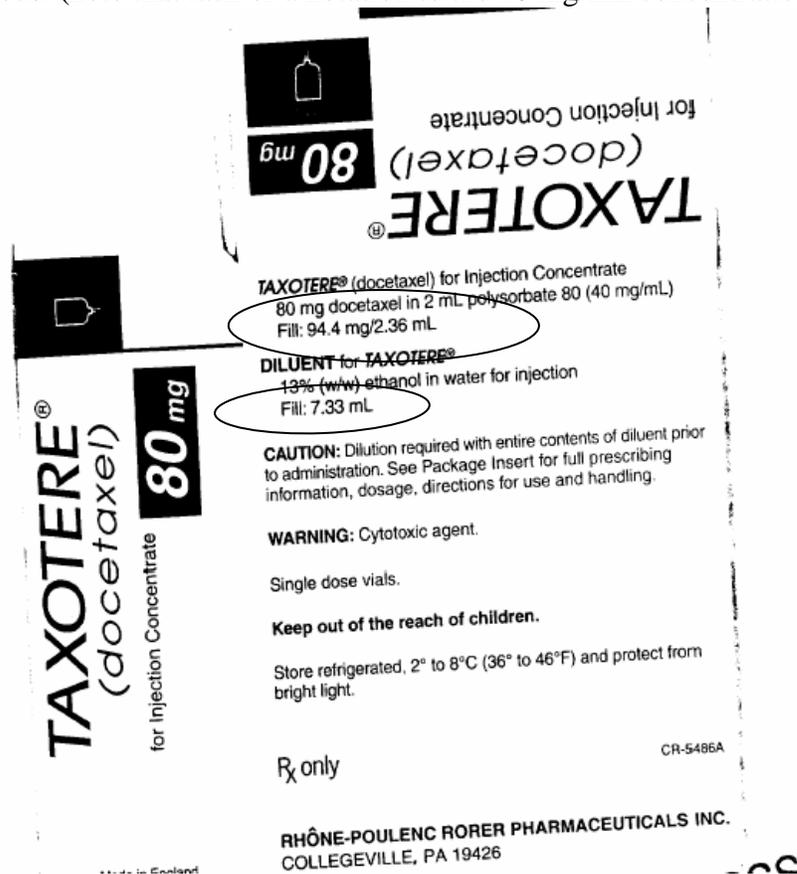
- Lack of Prominence of the Final Concentration

The final point of confusion was the lack of prominence of the final concentration (10 mg/mL) for the attention of the practitioners (n=3). This, in

turn, led to concentration confusion between 10 mg/mL concentration and the 20 mg/0.5 mL and 80 mg/2 mL strengths.

Updates to the labels and labeling appear to have minimized confusion, but DMETS notes that there is still concern with the lack of prominence of the initial dilution concentration from the time of approval. As many reporters from approval to the current date remain concerned that the documentation of the initial concentration is weak, DMETS has suggestions for unique color combinations to help increase the prominence of the initial concentration in Section IV. The following images detail carton and container with the subsequent changes.

Previous: (note that lack of a notation to the 10 mg/mL concentration)



Recently Approved:

Taxotere®

docetaxel

Injection Concentrate

Each TAXOTERE® Injection Concentrate Vial contains 20 mg/0.5 mL docetaxel in polysorbate 80.

Each DILUENT for TAXOTERE Vial contains approximately 1.8 mL of 13% (w/w) ethanol in water for injection.

Single-dose vials.

CAUTION: Withdraw the **entire** contents of diluent vial (approximately 1.8 mL) to dilute the Taxotere concentrate to achieve a docetaxel concentration of **10 mg/mL** for the initial dilution. Use **only** the required amount of the initial dilution to prepare the final infusion solution. See package insert for full dilution information.

10 mg/mL docetaxel after initial dilution.

Withdraw only the required amount needed of the 10 mg/mL docetaxel to prepare the final dilution for infusion.

Dosage and Administration: See package insert for dosage information, directions for use and handling.

WARNING: Cytotoxic agent. Keep out of reach of children.

Store between 2–25°C (36–77°F). Protect from bright light.

Mfd by: **Aventis Pharma Ltd.**

Dagenham, Essex RM10 7XS

United Kingdom

Mfd for: **Aventis Pharmaceuticals Inc.**

Bridgewater, NJ 08807 ©2005

Made in United Kingdom

www.aventis-us.com

50074855

6. Confusion between the proprietary names of Taxol and Taxotere (n=6)

The confusion between the proprietary names of Taxol and Taxotere was identified earlier by the FDA and addressed in multiple formats including a 2001 FDA Advise-Err and January 2003 FDA Patient Safety News. In addition, the name combination is present on the ISMP's List of Confused Drug Names. Upon review of cases, DMETS found six cases of confusion between Taxol and Taxotere with dates ranging from 2000 to 2005.

The etiology of the error is two-fold with the overt overlap in the leading four letters of "Taxo" and similar dosing. This may be compounded by their use in similar populations, by similar providers and under similar conditions. The earliest case (2000) describes the label as not having both the proprietary and established name and that as a corrective action, physicians would order by established names. The latest case (2005) notes the pharmacist misread the order due to similar names and doses with the added problem of the preprinted order sheets looking similar. This institution established a tall man protocol on the order sheets for the established names. A further case described the name similarity as playing a "significant role" in the infusion of the incorrect medication. This patient died five days after the infusion, but it was unclear of the causal relationship to the error as the patient was considered "debilitated with metastatic disease."

In another case, a medical resident made a computer selection error due to the system's method of using the first three letters to pull a name. The technician was unfamiliar with the products in an additional case, as the chemo log noted "Taxotere (Taxol)" after a shelf mispull of Taxol in lieu of Taxotere. One case was poorly documented with no indication of why the confusion occurred. The sixth and last case (2002) addressed that the label for Taxol acquired from the Pharmaceutical Management Branch of the National Cancer Institute did not denote the generic name. DMETS is unsure how applicable this is at this time.

DMETS believes this confusion should continue to be monitored in order to determine if alternatives need to be provided to prevent patient harm.

IV. LABEL AND LABELING RECOMMENDATIONS

Although the sponsor underwent a recent change to the Taxotere carton and container labels (May 11, 2005), DMETS remains concerned that these updates may be insufficient to combat the confusion with the strength and initial concentration. Thus, the following are recommendations to help alleviate confusion or potential confusion with the carton and container.

A. Container Label

1. DMETS believes the addition of an asterisk on the front panel to reference the back panel may help guide practitioners to the concentration after initial dilution. The following is an example of what we are suggesting:

80 mg/2 mL
Before Initial Dilution*
(b) (4)

2. As multiple practitioners were concerned with the lack of prominence of the final concentration, DMETS recommends a reverse color for the Caution statement. As currently presented, the statement is difficult to read and may be overlooked (especially with duplication of the red coloring of the 80 mg/2mL strength). However if the sponsor were to only color in red the bolded statements of "CAUTION", "entire", and "10 mg/mL", the reader's eye would be drawn to differences and potentially read the entire section. For the carton container the red coloring of the statement of "10 mg/mL docetaxel after initial dilution" may also serve to draw the reader's attention. See examples below:

Current presentation (20 mg/mL):

CAUTION: Withdraw the entire contents of diluent vial (approximately) 1.8 mL to dilute the Taxotere concentrate to achieve a docetaxel concentration of 10 mg/mL for the initial dilution. Use only the required amount of the initial dilution to prepare the final infusion solution. See package insert for full dilution

(b) (4)

10 mg/mL docetaxel after initial dilution.

Suggested presentation (20 mg/mL):

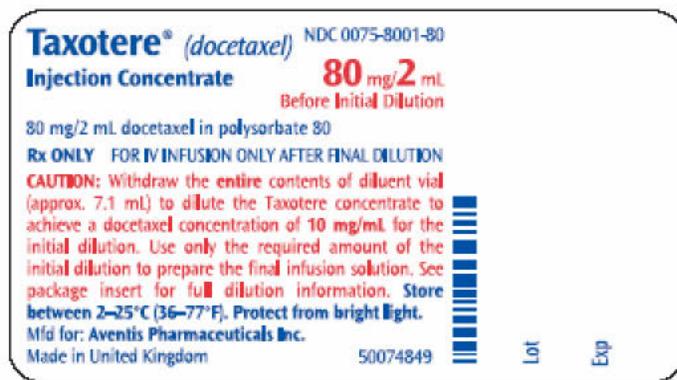
CAUTION: Withdraw the **entire** contents of diluent vial (approximately) 1.8 mL to dilute the Taxotere concentrate to achieve a docetaxel concentration of **10 mg/mL** for the initial dilution. Use only the required amount of the initial dilution to prepare the final infusion solution. See package insert for full dilution

(b) (4)

10 mg/mL docetaxel after initial dilution.

B. Container Label (Active Drug)

See Comment A 2 (see currently presentation below):



C. Container Label (Diluent)

1. DMETS recommends (b) (4)

2. DMETS recommends increasing the prominence of the net quantity to help assure proper identification of the diluent.

(b) (4)

In summary, DMETS recommends implementation of the labeling revision outlined in Section IV above. We would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Diane Smith at 301-726-0538.

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
Unk 8/13/1996 Unk PA	42048	Diluent Labeling Inadequate	Label	N/A	Diluent vial on Taxotere is labeled such that if it is partially turned the fact it's a diluent may not be noticed. Concern is that it may eventually lead to patient getting diluent only. Recommendation from reporter to USPC to prevent recurrence: This could be easily addressed by emphasizing the word "diluent" and centering it so it's seen - de-emphasizing drug name on the diluent vial.
Unk 8/23/1996 Unk N/A	122672	Concentration confusion Diluent	Label/labeling with diluent volume	N/A	Taxotere 80 mg vials come packaged with diluent that is labeled "13% Ethanol in water for injection"; "fill equals 7.33 mL". There is not 7.33 mL in this diluent vial (lot 6B344 Exp 6/97) of the product that the reporter prepared two days ago. The directions in the package insert for reconstitution of this product is vague. The reporter stated that there is great room for error in preparation of the product and the likelihood for inaccurate dosing.
Unk 9/5/1996 MI	1875115-2 23171	Concentration confusion	Label confusion with total vial content	Hosp	The vial and box are clearly labeled as 80 mg. Fine print states that 94.4 mg is actually in the vial. Patient was ordered 160 mg Taxotere. Two vials labeled 80 mg each were diluted, dispensed, and administered. Therefore, patient actually received 188.8 mg. Additional information per call to reporter on 9/4/96: The strength, 80 mg, is printed in white inside a red box on the box and on the label of the vial. In fine print on the back of the box, it states that the fill is 94.4 mg in 2.36 mL. The package insert goes into detail that the final concentration is 10 mg/mL. The prominence of the 80 mg on the vial automatically makes one assume that there is 80 mg in the vial after reconstitution. The patient was a 50-year-old female who developed shortness of breath, severe coughing, flushing of the upper chest, neck, and face, and runny eyes and nose. She also experienced an increase in blood pressure. She was treated with Benadryl injection and Dexamethasone 10 mg IV. The infusion, which had been stopped when the patient developed the symptoms, was completed after treatment. She had been pretreated with Dexamethasone. It was not determined whether the symptoms experienced by the patient were related to the dosage received or were an adverse reaction to the medication. The patient was to received 160 mg of Taxotere, but was inadvertently given 190 mg. The patient experienced dyspnea and a cough during the infusion. The infusion was stopped and the patient was given Benadryl and a steroid (unknown). The infusion was restarted, and the patient was discharged upon completion. The patient was later re-hospitalized with shortness of breath.

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
Unk 11/25/1996 OK Unk	1866196	Wrong Route	Unknown	Other	Taxotere was infused directly into the vein, rather than via port on an already established IV line. Patient developed a six inch red spot extending from the infusion site along the vein during the infusion. There was redness and swelling in the affected area. Heat (hot compress) was applied to the infusion site during and immediately after the infusion.
Unk 11/25/1996 OK Unk	1866193-5	Wrong Route	Unknown	Other	Taxotere was infused directly into the vein, rather than via port on an already established IV line. Patient developed a red spot about the size of a "half-dollar" around the infusion site during the infusion. There was redness and swelling in the affected area. Heat (hot compress) was applied to the infusion site during and immediately after the infusion.
Unk 5/9/1997 Unk Unk	50157	Concentration confusion	Lack of concentration on vial	Unk	In mixing the new product Taxotere, a potential labeling problem was noted. The label on the vial indicates the strength of the medication as 20 mg in 0.5 mL. When the diluent that is provided is added, the concentration is approximately 10 mg/mL, but the vial does not indicate the new concentration. This could lead to a dispensing error if all calculations were done using the 20 mg/0.5 mL information. The final concentration is indicated in the package insert.
8/11/1997 9/4/1997 South Africa 43 F	2000629	Administration confusion	Unknown	Other	Patient came on day 13 of cycle 6 for a count. Her test for cardiac evaluation were done and she erroneously was given cycle 7 on day 13 instead of day 22. Nausea, mucositis
Unk 8/12/1997 Unk Unk	24392	Concentration confusion	Label confusion with total vial content	N/A	The problem was observed on 8/8/97. Packaging is confusing. It is hard to determine the final concentration of the solution. The 20 mg vial contains 23.6 mg
Unk 8/12/1997 Unk Unk	24393	Concentration confusion	Label confusion with total vial content	N/A	The problem was observed on 8/8/97. Packaging is confusing. It is hard to determine the final concentration of the solution. The 80 mg vial contains 94.4 mg
Unk 2/9/1998 Unk Unk	125913	Concentration confusion	Label/labeling with diluent volume	N/A	Taxotere 80 and 20 mg vials are believed to be underfilled. Only 7.2 mL extracted from many vials and lots. Therefore cannot measure 9.4 mL (94 mcg) of drug for final use. Manufacturer states that problem is acceptable because of (b) (4) per guidelines. Also, the entire caps for two vials of Taxotere 80 mg came off when the reporter to removed the plastic cap.

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
Unk 5/28/1998 Unk N/A	126468	Concentration confusion Diluent	Label/labeling with diluent volume	N/A	Labeling for Taxotere 80mg diluent label indicates a fill amount of 7.33ml drug vial specifies 80mg of Taxotere in 2ml of polysorbate 80. Fill: 94.4 mg/2.36 ml *Actually after adding the 7.33 ml diluent to 80 mg Taxotere, the final one is 80 mg/8ml, or 10 mg/ml *This is very confusing & could lead to drug errors
Unk 8/5/1998	25461	Concentration confusion	Label confusion with total vial content	N/A	A pharmacist reported that the labeling of the two strengths is misleading and dilution information in the package insert is confusing. Using the diluent provided and following the manufacturer's instructions for dilution, the 20 mg vial actually contains 23.6 mg. and the 80 mg vial contains 94.4 mg. In the package insert under preparation, it reads that the premixed solution of Taxotere can be added to an infusion bag or bottle of 250 mL of 0.9% Sodium Chloride or 5% Dextrose solution. Later in the insert, it reads that DEHP may leach from PVC bags or infusion sets and only glass or polypropylene bottles, or plastic bags made of polypropylene or polyolefin should be used.
Unk 9/28/1998 Unk N/A	126918	Concentration confusion- diluent	Label/labeling with diluent volume	N/A	Insufficient amount of diluent supplied. Difficult, if not impossible, to obtain a final concentration of 10mg/ml.
Unk 12/11/1998 Unk N/A	127257	Concentration confusion	Lack of concentration	N/A	Taxotere order for 45mg IV. Taxotere box is labeled 80mg docetaxel in 2ml polysorbate 40mg/ml Fill 94.4mg/2.36ml Diluent for taxotere 13% (w/w) ethanol in water for injection Fill 7.33ml Technician diluted taxotere with diluent. Pharmacist checks the drawn up mixture of 1.1ml that came from the taxotere vial labelled 80mg docetaxel in 2ml (No where does it state by manufacturer the final concentration of 10mg/ml)
Unk 3/18/1999 Unk N/A	127581	Concentration confusion	Label confusion with total vial content	N/A	Taxotere 20mg & 80mg actually has more than 20mg and 80mg-has 23.6mg and 94.4mg respectively. Misleading packaging. However no adverse events have occurred.

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
Unk 4/23/1999	127725	Concentration confusion Diluent	Label/labeling with diluent volume	N/A	When diluent is added to the drug vial, the resulting volume is less than the labeled amount. The reporter has called the mfr. They seemed to be aware of this problem. He was advised the problem was "being addressed". They told him the minimum volume to assure a concentration of 10mg/1ml is 1.74 mL. On some vials, this concentration was not obtained. On others, the threshold was obtained, but a full 2 mL was not. Thus, the pharmacy is paying for product that it is not getting. With so much inconsistency in these vials, what is the accuracy of the concentration? The individual (Pharm D) who would normally take these types of reports was out of the office this week. He spoke to another company representative , but will follow-up next week to speak to the regular person.
Unk 5/21/1999 Unk N/A	127808	Concentration confusion Diluent	Label/labeling with diluent volume	N/A	With both strengths of Taxotere (80 mg and 20 mg), the required amount of diluent is unable to be withdrawn, (in my opinion due to a design flaw with the vial and stopper mechanism) yielding an unknown concentration of drug. Also the drug does not mix with the diluent to give an uniform mixture, to the point that there is separation after mixing in the time it takes to insert the needle in the vial and withdraw the contents.
(b) (4) 8/16/1999 Chile 59 M	3334894-8	Underdosing due to confusion with concentration	Lack of concentration	None	This 58-year-old male patient received cycle three of docetaxel in combination with cisplatin and fluorouracil for gastric cancer on (b) (6). On (b) (6) he was hospitalized with febrile neutropenia along with severe hyponatremia, hypocalcemia, thrombocytopenia and anemia. The investigator considers the serious event, febrile neutropenia, possibly related to the study drugs. Report 1 follow-up #1: manufacturer receipt date, 12 July, 1999. This patient was diagnosed with an infection on (b) (6). On (b) (6) he also had severe myocardial dysfunction. He was treated in the icu. On (b) (6) he died. The investigator considers the serious event, febrile neutropenia, possibly related to the study drugs. The investigator did not give a causality for the serious events of severe myocardial dysfunction, infection and death, however rpr considers these events reasonably associated to the study drugs. Report 1 follow-up # 2: manufacturer receipt date, august 11, 1999. Summary and clarification of events: the third cycle of chemotherapy was given on the (b) (6) Two days later an error was detected in the doses given (only 26mg of taxotere and 10mg of cddp were given) the dose was recalculated and given to complete 100% of the intended dose. The patient was discharged well on completion of chemotherapy. The patient was readmitted on june 26 with a moderate infection associated to severe

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
					leukopenia and antibiotic therapy was initiated (2 antibiotics) plus fluconazole and granocyte. In the following days thrombocytopenia became more severe; a central cath could not be installed. Peripheral access complicated by phlebitis and cellulitis. The patient was transferred to another hospital on (b) (6). During hospitalization patient presented with persistent hyponatremia. Cardiogenic shock was detected (echocardiogram showed severe cardiac dysfunction) and sepsis which did not improve with antibiotic therapy. This patient died on (b) (6). Cause of death has not been determined. The investigator considers the serious event, febrile neutropenia, as possibly related to the study drugs. The investigator also gave a causality for the serious events myocardial dysfunction, sepsis and death, as probably related to the study drugs.
Potential Error 7/13/1999 SD N/A	3301733-0	Diluent Labeling Inadequate	Label	N/A	Diluent label for Taxotere looks like active drug. No actual error took place yet but should be changed
Potential Error 3/16/2000 VA N/A	3476443-X 128869	Concentration Confusion	Label/labeling with diluent volume	N/A	If you had a physician order for taxotere 100mg how many ml of solution would you need? Enclosed boxes and package insert for you all to review/do calculations. This one has stumped 8 pharmacist here... Even after a call to the manufacturer. (look at strengths on box large & fine print and vials/package insert)./ We've been trying to get 7.33 mL of diluent out of one of these vials for a couple of weeks without success. Finally dawned on us this am that the needle "dead space" contained the missing 0.15 mL.
(b) (6) 8/28/2000 ID 52 M	3560664-1	Taxol	Unknown	Death	Physician ordered "Taxol 175mg/m ² x 1.5m ² =260mg" Pharmacy prepared "Taxotere 260mg" & nursing staff began infusion. Physician discovered error during infusion; patient received 183mg. Patient given Filgrastim 300mcg QD. Patient became more lethargic and HR increased (baseline 83-118 up to 128-150) over next 4 days. Patient expired (b) (6) am. The preparer of this report feels very strongly that this error was a result of the similarity in the names of these two products.

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
11/28/2000 12/11/2000 Unk Unk	3625650-1	TAXOL	Computer selection error	Not given	A physician ordered "Taxotere" 120mg IVPB over 1 hour. Pharmacy prepared Taxol 120mg instead. See pg 2 for additional information.
2/7/2001 2/21/2001 Netherlands Unk	3667794-4	Concentration Confusion Diluent	Label/labeling with diluent volume	N/A	Pharmacist realized that the reconstitution instructions for Taxotere(docetaxel) were not sufficient. He recommended that the manufacturer identify the correct volume of diluent to be placed into the drug contents, versus the instructions of "withdraw the contents of the diluent into a syringe..." Potential for error if the correct amount of volume is not added, due to concentration differences.
Unk 3/7/2001 Unk N/A	130818	Concentration confusion	Label/labeling with diluent volume	N/A	After adding supplied diluent to Taxotere 20mg vial and mixed according to package instructions, we are unable to remove the full dose/volume as labeled on the vial. It is then unknown if we are removing the correct concentration of the drug-may be less concentrated. It seems that a significant amount of the pre-diluted viscous drug dose not mix with the diluent and remains adhered to the vial. In addition even with gentle mixing, foaming does occur that slowly, if at all, breaks down. We are not confident that the dosing is accurate due to these factors. The drug representative from Aventis admits that this is a problem but offers no remedy.
3/30/2001 4/5/2001 Unk Unk	3698688-6	Inadequate Preparation Instructions	Labeling (PI)	N/A	The preparation instructions for taxotere are misleading. The product MUST be placed into a container that is non-PVC but this is not mentioned in the preparation instructions until after ALL of the reconstitution and preparation of the final product instructions.
(b) (6) 5/18/2001 GA 67 F	3727224-0	Wrong Route	Needle not place properly	Hosp	It involves a 67 year old female who received docetaxel 70 mg Aredia (pamidronate disodium) for breast cancer. Relevant medical history was not provided. Concomitant medications include Aredia. During the infusion, the needle was not in the vein and the medication infused into the lungs/pleural cavity. A chest tube removed 1.5 liters of fluid. The patient is in "bad shape" in ICU (Intensive Care Unit). The reporter did not provide a causality assessment. Additional information has been requested.

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
(b) (6) 12/21/2001 MO 43 F	3844255-0	TAXOL	Unknown	Hosp	Patient treated with Arm B of N9831. She completed AC on (b) (6) and was receiving weekly Taxol per protocol. On week #9 she received Taxotere instead Taxol due to a drug error. She was subsequently removed from N9831. (b) (6) patient began PO Keflex due to erythema and pain that started on her right knuckle and was tracking up her arm. She had burned herself on (R) Knuckle approx. (b) (6) Pt admitted to hospital for neutropenia and cellulitis on (b) (6) She was treated with IV Vancomycin and cefepime as well as Neupogen. Cellulitis resolved to bilateral patchy red dermatitis @ hands. Neutropenia resolved. Patient discharged to home (b) (6)
Unk 1/15/2002 NY Unk	3856929-6 132961	Diluent Labeling Inadequate	Label	N/A	Diluent vial for Taxotere does not have a volume indicated on the label; therefore there is not way to verify the correct content of the vial
4/17/2002 6/17/2002 Canada N/A	3934783-1	Concentration labeling concerns- TAXOL.....	Lack of established name on vial	N/A	I have recently received an investigational supply of Taxol(paclitaxel) from the Pharmaceutical Management Branch of the National Cancer Institute in the US. I have serious concerns about the manner in which this drug is labeled (ie/no generic name on the vials, vial content [30mg/5mL] more prominent than the mg/mL concentration). I believe that this is unsafe and may contribute to errors, given the confusion between this drug and docetaxel (Taxotere). Also, pharmacists and physicians are trained to rely on the generic names to potential errors.
Unk 5/13/2002 OH N/A	3916415-1 134024	Concentration confusion/labeli ng inadequate	Label/labeling with diluent volume	N/A	Product Package Insert for Taxotere (Docetaxel) by Aventis is poorly written-does not contain adequate information (Is misleading in regards to Preparation of Initial dilution. Recommendations for change are: (1) Description section should state: specific lot numbers of Taxotere concentrate and diluent are paired/package together for preparation of taxotere 10mg/mL, solution and are not interchangeable. this should be highlighted! (2) Description section should not state a volume for the Diluent vials as 1.5ml and 6.0ml This is misleading. (3) In preparation and administration section (A) PPI should state that Taxotere concentrate volume varies by manufacture lot number (B) Diluent volume to appropriately reconstitute taxotere concentrate to 10mg/ml varies by concentrate volume and is measured and provided by manufacturer for each taxotere concentrate vial. (C) Specific lots of Taxotere concentrate and diluent are packaged /paired together by manufacturer and are not interchangeable in the preparation of taxotere 10mg/ml initial dilution (D) When using multiple packages of Taxotere to prepare initial Taxotere dilution 10mg/ml use caution to use appropriate lots of diluent and concentrate as printed on packaging. Aventis

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
					should recommend a specific needle gauge to use during the entire preparation. (4) And the following to statement #3 of preparation and administration section when admined as instructed, a clear, homogeneous solution with no viscous or particulate matter should result.
5/20/2002 8/26/2002 Unk Unk	3966434-4	TAXOL	Name confusion	Unk	IV tech #1 to mix Taxotere chemo. IV tech #2 retrieved med from shelf. ___pulled Taxol instead of Taxotere. Taxol is located in chemo section of injectable; Taxotere is chemo section of refrigerator. IV tech #1 wrote in chemo preparation log, "Taxotere (Taxol)", which indicates she didn't recognize them as different products. Chemo mixed by IV Tech #1. Checked by pharmacist Pharmacy computer generated patient-specific label was for Taxotere (correct, as ordered), but Taxol was the med mixed. Dose of Taxotere was 43mg. Staff noted that they were busy, and pharmacist possibly interrupted during checking the drug.
Unk 8/26/2002 Unk N/A	134785	Refrigeration	Labeling (PI)	N/A	Labeling discrepancy. In the package insert under preparation and administration precaution #1 states Remove the appropriate number of vials of Taxotere from the refrigerator. On the box it states store between 2-25 degrees C. and protect from light, but nothing is stated about refrigeration.

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
(b) (6) 11/5/2003 Japan 64 M	4237419-8	TAXOL	Computer selection error from resident	Hosp	A 64-year-old male patient who was accidentally given docetaxel (Taxotere) instead of paclitaxel (Taxol) for lung cancer. Concomitant medications or the patient's relevant disease are not covered. The preceptor with ten-year experience and a resident with 5 months took in charge of the patient who was hospitalized in (b) (6). The patient was planned to receive "Taxol"; however, the resident input "Taxotere" in error on instruction on the computer. The computer has an automatic system that selects the drug based on the first three letters of the drug. The resident mistakenly clicked on Taxotere rather than Taxol. Preceptor has to confirm and sign the instruction. In this case, however, the instruction was sent to the department of pharmacy and the ward without the preceptor's signature. Then in (b) (6) unknown date), a nurse administered Taxotere by instillation (dose unknown) without entertaining any doubt as the drug was for anti cancer. Since the 7th day of the administration, the patient had white blood cell decrease, respiratory status aggravation, and circulatory organ abnormality. In this stage the preceptor and resident checked the instruction and noticed the error. The patient temporarily recovered; however, in the end of Sep pneumonia occurred and the patient died on (b) (6)
(b) (6) 12/3/2003 FI 79 M	4335287-7	Wrong Route	Unknown	Hosp	Initial report: This spontaneous postmarketing case, received from a physician who was also the patient, involved a male of unknown age who initiated therapy with Taxotere (docetaxel) weekly (unknown dose) (b) (6) ago for prostate cancer, exact therapy dates were not provided. About (b) (6) the patient received docetaxel subcutaneously in error, about 1-2 inches above his wrist. The infusion was discontinued as soon as the error was discovered; however, the patient's arm was swollen, his outside epidermis peeled, it was painful and red. The patient was hospitalized to receive IV antibiotics as oral antibiotics had no effect; the patient also received Percocet (oxycodone/acetaminophen) for pain. He had no fever and his white blood cell count was normal. The was patient was discharged from the hospital, but these events were ongoing. Therapy with docetaxel was discontinued. Medical history was significant for prostate cancer. Concomitant medication included cortisone. Reporter's assessment of causal relationship: Not provided. Addendum for follow up received 06-Apr-2004: Physician (the reporter and patient) provided his date of birth, weight and height. The 79-year-old male patient received Taxotere (docetaxel) for metastatic prostate cancer. He received chemotherapy IV and the product came out of his vein in the right wrist. He experienced severe pain in his wrist and hand and he was very sensitive to the cold. The reporter indicated that he wears

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
					<p>a glove on his right hand to keep the area warm. This event was ongoing. The reporter stated that he was told that his hand would get better but it could take a year. He had a port put in and had 3 additional treatments with docetaxel. A CBC done on an unknown date was normal and his PSA on an unknown date was 2600. Medical history was significant for a radical prostatectomy in (b) (6). A recent bone scan was negative and a recent abdominal and pelvic scan was positive. Addendum on 29-Oct-2003: The patient received docetaxel (Taxotere) 280mg on 4-Sep-2003 for primary lung cancer (Squamous cell carcinoma). Concomitant medications involve cisplatin (Briplatin), ramosetron hydrochloride (Nasea), dexamethasone (Decadron), mannitol, tegafur uracil (UFT), bicalutamide (Casodex), and prednisolone. The patient and prostate cancer, interstitial pneumonia, and hypertension as concomitant diseases and had no relevant medical histories. Epidose of treatment is as follows: When the patient was receiving a treatment for prostate cancer, abnormal opacity on right lung field was observed, which was diagnosed as primary lung cancer. On (b) (6) the patient visited the reporting hospital. As he was of non-operation applicable patient, radiation therapy and chemotherapy were employed for treatment. On (b) (6), the patient was hospitalized. On 3-Sep, radiation therapy was performed. On 4-Sep, chemotherapy was performed. On (b) (6) on early morning, an intense abdominal pain occurred. An examination revealed WBC 400 and CRP 31.85, a serious myelosuppression and systemic inflammation. A mild blood pressure decrease was observed too. The administration of G-CSF, steroid and stabilization of hemodynamic status were implemented. On the following day, WBC increased to 1,700 and general condition improved. On (b) (6), SPO2 markedly decreased, which was revealed on CT as an aggravation of interstitial pneumonia. The patient was brought to ICU. PsO2 decreased to 61mgHg even with the treatment with 100% oxygen administration via facemask F1 at 10 litters per minute. It was treated with steroid pulse therapy to the extent the patient did no longer need the oxygen inhalation. On (b) (6), Hb was being decreased to 6.5. Around 10:30pm, melaena with massive amount followed by haemorrhagic shock occurred. The patient was brought to ICU to be under the control of respirator. On (b) (6) the amount of haemorrhage was now 800 to 1,000ml per hour. An emergent angiogram and haemostasis were performed then haemorrhage was suppressed. However, an infection was complicated due to the re-aggravation of interstitial pneumonia and suppressed lung immune system. On (b) (6), late at night, gastrointestinal haemorrhage reoccurred and the patient again went under the control</p>

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
					of the respirator. Angiography did not reveal the exact size of haemorrhage. Treatment with a continuous infusion of vasopressin (Pitressin) was started. Haemorrhage was temporary suppressed. However, the patient complicated DIC and multi organ failure that led to the patient death, which was at (b) (6). Autopsy finding showed the cause of death is systemic haemorrhage. The reporting physician comments as follows: The patient had complicated interstitial pneumonia before the administration of chemotherapy. As far as gastrointestinal haemorrhage is concerned, docetaxel (Taxotere) which has strong invasion to mucus is probably associated to the event. It is also considered that using a great amount of steroid of long duration for interstitial pneumonia resulted in mucosal disorder. The patient's general condition, which had been reduced due to the aggravation of interstitial pneumonia and other symptoms, cannot be ruled out of causality with the event. The reporting physician assesses the causality between docetaxel (Taxotere) and the two events, the aggravation of interstitial pneumonia and gastrointestinal haemorrhage, as "probable."
11/11/2003 11/12/2003 IL Unk	4235187-7 138355	Concentration confusion	Label	N/A	The included packaging. Rx tech went to compound Taxotere-? over correct volume to use as front of package highlights conc = 20 mg/0.5 mL. On reading packaging in detail it states conc after dilution actually 10 mg/mL = 20 mg/2mL. Aventis was called and notified of potential error concerns- said packaging change was FDA mandated. This report is to register safety concerns with the FDA especially for potential for error in facilities w/ lack of experienced/low volume compounding of Taxotere.
11/26/2003 12/23/2003 Unk Unk	4258157-1	Concentration confusion	Label	N/A	The new packaging for docetaxel, Taxotere. The box has the following labeling "Taxotere , docetaxel injection concentrate 20 mg/ 0.5 mL". This packaging is very misleading. While it may be true that the concentrate is 20 mg/ 0.5 ml prior to dilution, once the product is diluted, it has a final concentration of 10 mg/ 1 mL.
2/3/2004 3/12/2004 Unk N/A	4316843-9	Concentration confusion	Label	N/A	The box label changed from reading "80 mg" to "80 mg/2ml". This "80 mg/2ml" is prior to dilution. After dilution the concentration is "10 mg/ml". This could cause confusion after the correct volume to use when preparing admixture.

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
1/23/2004 3/12/2004 PA Unk	4316758-6	Concentration confusion	Label	Unk	We had an order for an inpatient for weekly taxotere -- 60 mg/dose. The third dose was ordered today and when the pharmacist was building the order, was comparing the current dose to the ordered dose 1 week ago. 1 week ago, the pharmacist had used 6 mL of drug to make the dose of 60 mg. Today, the pharmacist, seeing the 80 mg/2 mL, was concerned that there had been a drug error 1 week ago -- giving the patient 240 mg instead of 60 mg. After further research, we found the 80 mg/8 mL diluted concentration and that the front is actually saying that 80 mg and 2 mL of diluent is provided. We realized that the front of the packaging had led to today's confusion.
1/28/2004 3/11/2004 NJ N/A	4315403-3	Concentration confusion	Label	N/A	I'd like to report a concern regarding new packaging of Taxotere (docetaxel injection, Aventis). The product is packaged as a vial of concentrate containing 80 mg in 2 ml which must be further diluted with the enclosed diluent (7.1 ml) for a final concentration of 10 mg/ml (ml volume). The new outer packaging states "Taxotere Injection Concentrate 80 mg/2 ml." While this is true for the concentrated injection, my concern is that once diluted as directed, the final product is 10 mg/ml, not 40 mg/ml. Example: When diluted appropriately, a dose of 60 mg would require 6 ml of the diluted solution. If the concentration of the dilution was misinterpreted as 40 mg/ml instead of 10 mg/ml, a dose of 60 mg would use only 1.5 ml of the diluted solution, resulting in a significant underdose as 1.5 ml would only contain 15 mg. The previous packaging stated Taxotere 80 mg on the outer carton, with specific dilution instructions inside. Although the new package has clear instructions on the back, I feel this new packaging could lead to confusion, particularly for healthcare professionals who may not be familiar with this agent.
1/29/2004 3/11/2004 Unk Unk	4315392-1	Concentration confusion	Label	N/A	The overwrap containing the drug and diluent vials lists the Taxotere conc as 80 mg/2 ml in large red letters at the top of overwrap. The diluent is listed but w/o a volume. Further down on the overwrap a caution warning. CAUTION: Withdraw the entire contents of diluent vial (approx 7.1 ml) to dilute the Taxotere concentrate to achieve a docetaxel concentration of 10 mg/ml in the initial dilution. Use only the require amount of the initial dilution to prepare the final infusion solution. See package insert for full dilution information. It is not initially clear what the concentration is. Someone could see the 80 mg/2 ml and consider that the conc. After initial dilution and thus the patient would be underdosed. Recommendation: Keep the red 80 mg but delete (or put in package insert the 2 ml volume. This way it would be clearer that the total amount of drug is only 80 mg.

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
2/17/2004 5/3/2004 ME N/A	4352134-8	Concentration confusion	Label	N/A	Aventis has labeled Taxotere as 80 mg /2 ml on the box and on the vial in bold red but the product is diluted to 10 mg/mL.
3/18/2004 5/26/2004 CT N/A	4366811-6	Concentration confusion	Label	N/A	No patient harm came to this however this packaging problem can cause issues in the future!!!! Taxotere (docetaxel) manufactured by Aventis NDC: 0075-8001-80 has a mislabeled product package. It states the injection concentration is 80 mg/2ml when in fact after diluting the product with the diluent provided the concentration is 10 mg/ml. Very confusing and a potential for med errors !!!
Unk 3/30/2004 PA N/A	4326761-8 139591	Concentration confusion	Label	N/A	pharmacists and pharmacy technicians may be confused when reading these products labels, which could lead to making error when preparing and dispensing these products of Aventis: Docetaxel 20mg and 80mg. The concentrations of the concentrated docetaxel written in the front of the boxes may be confused with the concentrations of the final solution which are written in the back of the boxes under caution section.
4/27/2004 6/17/2004 NJ Unk	4381015-9	Concentration confusion	Label	N/A	Taxotere (docetaxel) was ordered as 80mg in 250mL NSS to be administered over 1 hour. In preparation, the Pharmacist wrote the instructions: "use 80mg/2mL vial and dilute with diluent vial included in the package". The Pharmacist then reconstituted with the 7.1mL of diluent provided (making a 10mg/mL solution). The Taxotere (docetaxel) vials have 80mg/2mL stamped on them, making it confusing once diluted with provided diluent. After dilution, this Pharmacist removed only 2mL out the vial (20mg), following the concentration on the vial, instead of the 8mL required due to the new concentration of 10mg/mL.
11/15/2004 1/11/2005 CA 71 M	4553855- 4/141910	Concentration confusion	Label	Unk	Wrong dose of docetaxel given to patient, labeling on box contributed to error. Front of box in large letters reads 80 mg/2 mL, the back of box reads in very tiny letters 10 mg/mL pt received wrong dose.

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
Unk 2/4/2005 PA Unk	4578617-3 142032	Concentration confusion	Label	N/A	Patient ordered Taxotere 35 mg one time. Prepared using 20 mg product, Labeled as 20 mg/0.5 mL Concentrate Vial and 80 mg/2 mL Concentrate Vial -Concentrate vial must be diluted w/ special diluent to prepare a final concentration of 10 mg/mL. While checking the chemotherapy, the Pharmacist was confused as to how much drug was needed for the 35 mg dose. They thought the first bag prepared by the technician incorrectly -3.5 mL of 2x20 mg products was used-. So they ended telling the technician to prepare another bag using 0.88 mL of the 80 mg/2ml product. The technician diluted the product and put 0.88 mL in- or approximately 9 mg-. The error was discovered and the patient received the correct total dose.
3/9/2005 5/9/2005 PA N/A	4658737-5	Concentration confusion	Label	N/A	Taxotere box label is misleading. Front of box and 2 sides list concentration as drug is provided in box (80 mg/2 ml). The Caution statement to dilute the medication appears only on the back of the carton.
3/9/2005 5/9/2005 FL	4658734-X	Concentration confusion	Label	Unk	Full dose of chemotherapy, docetaxel (Taxotere) was not prepared as ordered for patient being treated for squamous cell lung cancer. Patient received dose as prepared. This was the third course of therapy. Patient also receiving concomitant Carboplatin. Taxotere 80 mg is packaged together as two vials. One vial contains approximately 7.1 ml of diluent, and the other vial contains 2 ml (80 mg) of active drug. After dilution, the second vial contains 10 mg/ ml. Thus 13.5 ml of solution, after dilution, would have been required to obtain the 135 mg ordered dose. The vial with active drug is clearly labeled 80 mg/ml. A much smaller footnote reads that the vial will have a concentration of 10 mg/ml after dilution. The pharmacy technician, however, believed that vial contained 80 /2 ml after dilution, and only withdrew 3.375 ml, mistakenly believing that this would yield the 135 mg dose. The pharmacist checked the prescription prior to dispensing, but focused mainly on the vials used to prepare the solution. Unfortunately, both the active drug vial, and the diluent are labeled 80 mg/2 ml, and thus the pharmacist believed that enough drug was prepared. The syringe volume was not positively verified, and/or overlooked.

Event Date FDA Receipt Date Location Patient Age/Gender	AERS/ DQRS Number	Type	Cause	Patient Outcome	Narrative
7/7/2005 7/22/2005 NY 59 F	4724324-3	Administration confusion		Hosp	Chemotherapy was given with a pre-treatment Hgb of 7.2. Gemcitabine and Docetaxel were given on Day 1 instead of Gemcitabine only. Patient was subsequently admitted for blood transfusion, 2uprbc. Patient was discharged without incident after transfusion. On (b) (6) she presented to ER w/ hematemesis (grade 1)HCT 33% treated with IV fluids. EGD shows ulcer of gastric mucosa biopsy negative for tumor. CT Scan shows increase (from prior scan 6/23/05) in pancreas mass with possible stomach invasion. Discharged (b) (6) Hct 29%Patient has refused further treatment.
8/18/2005 11/4/2005 IN Unk	4821408-6	TAXOL	Order misread	No harm	On 8/18/05 an oncology patient was supposed to receive Taxotere 36 mg IVPB but wrongly received Taxol 36 mg. The physician's order was misread by the pharmacist and the patient received the wrong medication. The physician was notified and no known harm was done to the patient. No known harm was done to the patient. The fact that the drug names and doses are so similar greatly contributed to the error. The preprinted order sheets for Taxotere and Taxol look very similar.
9/7/2005 10/4/2005 POLAND 76 M	4800086-6 4860745-6	Unspecified overdose	Unknown	Hosp	This case involves a 77 year old male patient (weight 81 kg) who received therapy with docetaxel 120 mg (cumulative dose 1160 mg) from 18-Feb-05 (last date of therapy not reported), and Oblimersen 567 mg (cumulative dose 37730 mg) from 14-Feb-05 to 29-Aug-05 for treatment of prostate cancer. Relevant medical history and concomitant medication was not reported. This patient received overdose of docetaxel by mistake (no required dose reduction) in cycle 3 and cycle 4, then no subsequent dose 2 level reduction of docetaxel in cycle 5, 6, 7, 8, and 9. After cycle 9, a diagnosis of acute leukemia was made. Treatment is described as supportive (not specified). The event is ongoing. Patient was withdrawn from the study. The investigator's causal assessment: Probably related to study medication./

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Frank Cross

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