APPLICATION NUMBER:
022234Orig1s000

MEDICAL REVIEW(S)
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<td>Kristen M. Snyder, MD</td>
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<td>Clinical Team Leader</td>
<td>Patricia Cortazar, MD</td>
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Clinical Review
Kristen M. Snyder, MD
NDA 22234
Docetaxel

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Reference ID: 2901938
1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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

The exclusivity of the indications below has expired.

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

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

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

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

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

No new clinical data was submitted for this NDA. The Taxotere NDA 20449 has been previously reviewed for efficacy and safety. Therefore, the medical reviewer recommends approval for all of the above indications. The recommendation for the application is approval with respect to the
1.2 Risk Benefit Assessment

Please refer to NDA 20449.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: docetaxel

Proprietary Name: Docetaxel Injection

Applicant: Hospira, Inc.
275 North Field Drive
Bldg. H2-2, Dept. 389
Lake Forest, IL 60045
Tel: (224) 212-6158
Fax: (224) 212-5401

Drug Class: Disruptor of microtubule network

Proposed Indications:

Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC.

Non-Small Cell Lung Cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC.

Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer.
Proposed Dosage and Administration

Administered IV over 1 hr every 3 weeks for the following cancers:

- BC, locally advanced or metastatic: 60-100 mg/m^2 single agent
- BC adjuvant: 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles
- NSCLC: chemotherapy-naïve: 75 mg/m^2 followed by cisplatin 75 mg/m^2
- HRPC: 75 mg/m^2 with 5 mg prednisone twice a day continuously

Reviewer: The pediatric use information for the reference listed product (RLP) is based on data submitted in response to a pediatric written request is protected by Pediatric Exclusivity under the Best Pharmaceuticals for Children Act (BPCA) until May 13, 2013. While the innovator product was issued a pediatric written request, fairly complied with the terms of the WR, and received pediatric exclusivity no pediatric indication was sought. The labeling provides information regarding safety and dosing (including dose-limiting toxicity). Similarly, the question of whether pediatric language in labeling should be “carved-out” or retained in 505(b)(2) applications resulted in a consult to the Pediatric and Maternal Health staff regarding another 505(b)(2) application (NDA 200795) and its RLP (Gemcitabine). The Best Pharmaceuticals for Children Act (BPCA) does not address the protected pediatric information of 505(b)(2) products, only generic products. Therefore, the PMH staff believes omitting pediatric language may be appropriate for a 505b2 product when removal of the language will not result in a safety concern for pediatric patients.

Because the RLP (Taxotere) is not indicated for use in the pediatric population and toxicities seen in pediatric patients were similar to those seen in adults, Docetaxel Injection, if used in the pediatric oncology population, is unlikely to pose a significant or unknown safety risk.
Clinical Review
Kristen M. Snyder, MD
NDA 22234
Docetaxel

Premedication Regimen
• Oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice a day) for 3
days starting 1 day before administration
• HRPC: oral dexamethasone 8 mg at 12, 3, and 1 hr before treatment

For dosage adjustments during treatment see full prescribing information.

Dosage Forms and Strengths
• 20 mg/2 mL single-dose vial
• 80 mg/8 mL multi-dose vial
• 160 mg/16 mL multi-dose vial

Contraindications
• Hypersensitivity to docetaxel injection or polysorbate 80
• Neutrophil counts of <1500 cells/mm³

Warnings and Precautions
• Acute myeloid leukemia
• Fetal harm can occur when administered to a pregnant woman. Women of childbearing
  potential should be advised not to become pregnant when taking Docetaxel Injection
• Asthenia

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

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

2.3 Summary of Resubmission Regulatory Activity Related to Submission
None

2.4 Pediatric Waiver
Pediatric exclusivity of Taxotere ended on November 14, 2010.
2.5 Other Relevant Background Information

Patent Infringement Case

At the time of NDA filing with the FDA Hospira cited “Paragraph IV” alleging that U.S. Patent Numbers 5438072, 5698582, 5714512, and 5750561 were invalid, not infringed, and/or not enforceable. In court proceedings sanofi-aventis sued Hospira for infringement of patents ‘512 and ‘561 and lost. They did not challenge Hospira’s paragraph IV citations for patents ‘072 or ‘582 (see Appendix 7.4)

Table 1: Patent Data for TAXOTERE Injection Concentrate

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<tr>
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Table 2: Exclusivity Data* for TAXOTERE Injection Concentrate

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<td>I-436</td>
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<td>I-542</td>
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3 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to NDA 20449 CMC, Pharmacology/Toxicology, and Clinical Pharmacology reviews, NDA 201525 CMC review, and the label.

4 Sources of Clinical Data

Refer to NDA 20449.

5 Review of Efficacy

Refer to NDA 20449.

6 Review of Safety

Refer to NDA 20449.

7 Appendices

7.1 Literature Review/References

Refer to NDA 20449.

7.2 Labeling Recommendations

See final label. The clinical safety and efficacy are based on the Taxotere (NDA 20449) label. The clinical team is inagreement with the final approved labeling, carton and container labels.

7.3 Advisory Committee Meeting

None

7.4 Patent Infringement Case

Sanofi's initial case:\nhttp://www.orangebookblog.com/Aventis_20v._20Hospira_20_28Taxotere_29_20complaint.pdf

Outcome: Sanofi's Taxotere Patents Found Invalid2
Sanofi filed an infringement action against Hospira and Apotex in November 2007 alleging that the companies infringed U.S. Patent Nos. 5,714,512 and 5,750,561 by filing NDAs for docetaxel (see "Court Report," November 18, 2007). In November 2009, following a bench trial in the U.S. District Court for the District of Delaware, the parties were ordered to present post-trial proposed findings of fact and conclusions of law concerning the validity and enforceability of the '512 and '561 patents.

On September 27, 2010 Judge Gregory Sleet ruled that the defendants had established by clear and convincing evidence that Sanofi's '512 and '561 patents were invalid due to indefiniteness and obviousness, and unenforceable due to inequitable conduct. In a lengthy opinion, Judge Sleet found that the specific formula for Taxotere was obvious in view of U.S. Patent No. 4,814,470, which issued in 1989. Judge Sleet also found that Sanofi did not disclose two highly material prior art references to the Patent Office during the prosecution of the '512 and '561 patents, thus rendering them unenforceable3.

References

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/s/

------------------------------------------
KRISTEN M SNYDER
02/07/2011

PATRICIA CORTAZAR
02/08/2011

Reference ID: 2901938
| **Proposed Indications** | Breast Cancer  
  • Docetaxel Injection is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.  
  • Docetaxel Injection in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.  
  
  Non-Small Cell Lung Cancer  
  • Docetaxel Injection as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.  
  • Docetaxel Injection in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.  
  
  Prostate Cancer  
  • Docetaxel Injection in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer. |

<p>| <strong>Action:</strong> | Tentative Approval |</p>
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SEALD=Study Endpoints and Labeling  
OSE= Office of Surveillance and Epidemiology  
DMEPA= Division of Medication Error Prevention and Analysis  
DDRE= Division of Drug Risk Evaluation  
CMC= chemistry manufacturing and controls
1. Introduction

This is a 505(b)(2) application for docetaxel injection submitted by Hospira, Inc. The major differences between Sanofi-Aventis’ Taxotere® and Hospira’s product are as follows:

a) The Hospira product can be directly diluted into infusion solutions, as compared to Taxotere®, which must be diluted to a strength of 10 mg/mL prior to addition into infusion solutions.

b) Hospira, Inc. is registering an additional presentation (160 mg/16 mL) that the innovator does not have.

c) Hospira, Inc. is proposing a multi-dose application for the 80 mg/8 mL and 160 mg/16mL presentations as compared to Taxotere® which is supplied as single-dose vials.

Although Taxotere® is approved for indications in the treatment of breast cancer, non-small cell lung cancer, prostate cancer, squamous cell carcinoma of the head/neck, and gastric/GE junction adenocarcinoma, exclusivity for the head/neck cancer and gastric/GE junction indications does not expire until 2009. Therefore, the Hospira indications in the tentative approval letter will be limited to breast cancer, lung cancer, and prostate cancer.

2. Background

Please see above.
3. CMC

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance.

The CMC primary review was completed and archived by Terrance Ocheltree, R.Ph., Ph.D. and also signed by Ravi Harapanhalli, Ph.D. on 7/24/08.

The following is excerpted from the CMC review:

“...The recommendation for the application is approval with respect to the chemistry, manufacturing, and controls (CMC). The sites recommendation from the Office of Compliance is listed in EES as acceptable. The applicant and Holder of the Type II Drug Master File (DMF) referenced in the NDA have adequately responded to all CMC issues outlined in either this review or the review for DMF [b] [b] [b] [b] [b]. All CMC comments related to the carton and container labels have either been implemented or satisfactorily addressed.

The following comment should be included in the action letter.

1. An expiration dating period of [b] [b] [b] [b] is granted to your product. You may extend the expiration date based on satisfactory accrual of real time stability data and report it in the annual report.
2. We remind you of your letter dated 11-MAR-2008 in which you have indicated that the [b] [b] [b] [b] [b] has been withdrawn. Therefore, any future site change should be submitted as a prior-approval supplement to the NDA.”

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharm/tox issues that preclude approval. The review was completed and archived by Margaret Brower, Ph.D. and Haleh Saber, Ph.D. on 6/9/08.
5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval. The review was completed by Sophia Abraham, Ph.D. and also signed by Brian Booth, Ph.D. on 10/1/07.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewers that there are no outstanding clinical microbiology or sterility issues that preclude approval.

The initial microbiology review, completed by Anastasia G. Lolas, Ph.D. on 4/11/08 identified several deficiencies. Specifically, additional information was required and requested for the process of depyrogenation of vials, efficacy of the to remove bacterial endotoxins, procedures and specifications for media fills, and for the summary of antimicrobial effectiveness test results. The request was sent on 4/11/08 and a response was received on 4/25/08. The response was considered to be a major amendment.

A subsequent review recommending approval was completed and archived by Anastasia Lolas, Ph.D. and Bryan Riley, Ph.D. on 6/9/08. The applicant’s responses were considered acceptable.

7. Clinical/Statistical-Efficacy

There were no new clinical data submitted with this 505(b)(2) application.

The medical review, archived by Qin Ryan, M.D., Ph.D. on 8/7/08 recommends “...approval ...when the exclusivity for Taxotere® expires.”

The medical review team had several labeling recommendations including minor changes to section headings for breast cancer and prostate cancer to more specifically reflect the approved indications, rounding off estimates of adverse reactions to the nearest whole number, and changing “Docetaxel injection” to “docetaxel” throughout the proposed label.

The medical review team agreed with the recommendation to add a patient counseling section as recommended by the SEALD team.
8. Safety

The office of surveillance and epidemiology recommended strategies to reduce the potential risk of medication errors arising from the differences in preparation between this final product and Taxotere®. However, it should be noted that this product can be directly diluted into infusion solutions, as compared to Taxotere® which must be diluted to a strength of 10 mg/mL prior to addition into infusion solutions. Therefore, the risk of a medication error is small, and an error is not likely to result in a change in dosing.

After internal discussion between OSE staff, the CMC review team, and the clinical review team, the following approach was adopted:

   a. propose that the applicant further enhance the prominence of the route of administration statement “For IV infusion only” on the carton labeling. (This was agreed to by the applicant on 8/8/08)

   b. propose that the applicant agree to inform healthcare practitioners about the differences in the preparation of the proposed Docetaxel Injection versus other docetaxel products (e.g., Dear Healthcare Professional letter). (This was agreed to by the applicant on 8/8/08)

9. Advisory Committee Meeting

An advisory committee meeting was not considered necessary given the substantial evidence of safety and effectiveness and post-marketing information available on the active ingredient, docetaxel.

10. Pediatrics

Pediatric waivers for the proposed indications have been submitted. The PeRC will discuss these at the next scheduled PeRC and approval of the waivers is anticipated.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.
12. Labeling

See specific discipline reviews.

13. Decision/Action/Risk Benefit Assessment

The application is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed upon labeling. This determination is contingent upon information available to the Agency at this time and is, therefore, subject to change on the basis of any new information that may come to our attention.

The listed reference drug product is subject to a period of patent protection and exclusivity protection and therefore, final approval of the application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired, i.e., September 28, 2010.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ramzi Dagher
8/11/2008 09:37:17 AM
MEDICAL OFFICER
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<td><strong>Reviewer Name</strong></td>
<td>Qin Ryan, MD, PhD</td>
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<td><strong>Clinical Team Leader</strong></td>
<td>Amna Ibrahim, MD</td>
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<td>Ramzi Dagher MD</td>
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<td><strong>Therapeutic Class</strong></td>
<td>Microtubule disregulator and antineoplastic</td>
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<td><strong>Intended Population</strong></td>
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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This NDA for docetaxel injection in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act was submitted to request approval of therapeutic equivalence of the proposed product to Taxotere, as defined in the FDA orange book. The sponsor of NDA 20449 for Taxotere is sanofi-aventis. The exclusivity of indications below will be expired on August 10, 2008:

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

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

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

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

1.2 Risk Benefit Assessment

Please refer to NDA 20449.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: docetaxel
Proprietary Name: Docetaxel Injection

Applicant: Hospira
275 N. Field Dr.
D-0389, Bldg. H2-2N
Lake Forest, IL 60045-5046

Drug Class: Microtubule disregulator and antineoplastic

Proposed Indications:

Breast Cancer (BC): single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC.

Non-Small Cell Lung Cancer (NSCLC): single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC.

Hormone Refractory Prostate Cancer (HRPC): with prednisone in androgen independent (hormone refractory) metastatic prostate cancer.

Proposed Dosage and Administration

Administered IV over 1 hr every 3 weeks for the following cancers:

- BC, locally advanced or metastatic: 60-100 mg/m2 single agent.

- BC adjuvant: 75 mg/m2 administered 1 hour after doxorubicin 50 mg/m2 and cyclophosphamide 500 mg/m2 every 3 weeks for 6 cycles.

- NSCLC: after platinum therapy failure: 75 mg/m2 single agent

- NSCLC: chemotherapy-naïve: 75 mg/m2 followed by cisplatin 75 mg/m2

- HRPC: 75 mg/m2 with 5 mg prednisone twice a day continuously

Premedication Regimen

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

- HRPC: oral dexamethasone 8 mg, at 12, 3, and 1 hrs before treatment
Dosage adjustments during treatment see full prescribing information

**Dosage Forms and Strengths**
- 20 mg/2 mL single-dose vial
- 80 mg/8 mL multi-dose vial
- 160 mg/16 mL multi-dose vial

**Contraindications**
- Hypersensitivity to Docetaxel Injection or polysorbate 80
- Neutrophil counts of <1500 cells/mm$^3$

**Warnings and Precautions**
- Acute myeloid leukemia
- Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant when taking Docetaxel Injection
- Asthenia

**Adverse Reactions**
Most common adverse reactions are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, myalgia

**2.2 Availability of Proposed Active Ingredient in the United States**
Taxotere is marketed in the US.

**2.3 Summary of Presubmission Regulatory Activity Related to Submission**

July 9, 2007: Hospira submitted NDA 22234.

**2.4 Pediatric Waiver**
A full pediatric waiver request was submitted with NDA 22234 submission. The waiver is granted because there are very few pediatric patients, if any, that would have breast cancer, lung cancer or prostate cancer.

**2.5 Other Relevant Background Information**
Refer to NDA 20449

*Table 1: Patent Data for TAXOTERE Injection Concentrate*
3 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to NDA 20449 and the label.

4 Sources of Clinical Data

Refer to NDA 20449.

5 Review of Efficacy

Refer to NDA 20449.

6 Review of Safety

Refer to NDA 20449.

7 Appendices

7.1 Literature Review/References

Refer to NDA 20449

7.2 Labeling Recommendations

The clinical recommendations for the label are as follows:

<table>
<thead>
<tr>
<th>Exclusivity Code</th>
<th>Exclusivity Definition</th>
<th>Exclusivity Expiration</th>
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<tbody>
<tr>
<td>I-429</td>
<td>For use in combination with prednisone for the treatment of patients with androgen</td>
<td>19 May 2007</td>
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<tr>
<td></td>
<td>independent (hormone refractory) metastatic prostate cancer.</td>
<td></td>
</tr>
<tr>
<td>I-436</td>
<td>For use in combination with doxorubicin and cyclophosphamide for the adjuvant</td>
<td>18 Aug 2007</td>
</tr>
<tr>
<td></td>
<td>treatment of patients with operable node-positive breast cancer.</td>
<td></td>
</tr>
</tbody>
</table>

* No exclusivity information remain in Orange Book for NSCLC indication.
• Administrative revision of adverse reaction observed during treatment for breast cancer
• Round off adverse event incidence.
• 14.1 title changed to “locally advanced or metastatic breast cancer”.
• (NSCLC) was removed from 14.3 title.
• 14.4 title changed to “Hormone refractory prostate cancer”
• All “Docetaxel Injection” phrases changed to “docetaxel”.
• Please also see chemistry and clinical pharmacology reviews for relevant label changes.

7.3 Advisory Committee Meeting

None
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Qin Ryan
8/7/2008 10:43:56 AM
MEDICAL OFFICER

Ramzi Dagher
8/7/2008 12:06:47 PM
MEDICAL OFFICER