European Medicines Agency
Evaluation of Medicines for Human Use

London, 24 September 2009
Doc. Ref.: EMA/774985/2009

ASSESSMENT REPORT
FOR

Docetaxel Winthrop

International Nonproprietary Name: **docetaxel**

Procedure No. EMEA/H/C/000808/X/0008

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Aventis Pharma S.A. submitted on 3 December 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Docetaxel Winthrop 20 mg/1ml and 80 mg/4ml concentrate for solution for infusion, pursuant to Annex II, point 2 iii and iv of the Commission Regulation (EC) No 1085/2003.

Aventis Pharma S.A. is the Marketing Authorisation Holder for Docetaxel Winthrop 20 mg and 80 mg concentrate and solvent for solution for infusion authorised on 20 April 2007 as an informed consent application in accordance with Article 10c of Directive 2001/83/EC, as amended. The consent from the MAH of the Taxotere application, which had been submitted as a full application under Art 8(3) of Directive 2001/83/EC as amended, has been given allowing access to the initial dossier of the product.

The Rapporteur appointed by the CHMP and the evaluation teams was: Pierre Demolis

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 3 December 2008.
- The procedure started on 24 December 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 March 2009.
- During the meeting on 20-23 April 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 April 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2009.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 2 July 2009.
- During the CHMP meeting on 20-23 July 2009, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 August 2009.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 16 September 2009.
- During the meeting on 21-24 September 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Docetaxel Winthrop on 24 September 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 21 September 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Docetaxel Winthrop concentrate and solvent for solution for infusion contains docetaxel (active substance), which is an antineoplastic agent that enters tumour cells and disrupts intracellular structures necessary for the replication and survival of these cells. Docetaxel acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly, which leads to a marked decrease of free tubulin and eventually to cancer cell death. The binding of docetaxel to microtubules does not alter the number of protofilaments.

The approved therapeutic indications for Docetaxel Winthrop are:

Breast cancer

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

Docetaxel Winthrop in combination with doxorubicin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.

Docetaxel Winthrop monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent.

Docetaxel Winthrop in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 and who previously have not received chemotherapy for metastatic disease.

Docetaxel Winthrop in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.

Non-small cell lung cancer

Docetaxel Winthrop is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.

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

Prostate cancer

Docetaxel Winthrop in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer.

Gastric adenocarcinoma

Docetaxel Winthrop in combination with cisplatin and 5 fluorouracil is indicated for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease.

Head and neck cancer

Docetaxel Winthrop in combination with cisplatin and 5 fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.

Docetaxel is prepared by semi-synthesis using a substance extracted from yew needles, i.e. 10-deacetylbaccatin III (DAB-10).

Currently Docetaxel Winthrop is available as a two-vial formulation and it is supplied as a vial containing a concentrated solution of docetaxel in polysorbate 80 with citric acid requiring dilution in a diluent containing ethanol/water mixture. For administration, the concentrated solution and the diluent are first mixed to obtain a solution (or premix), which is used for preparation of a solution for infusion.

The present application supports a line extension for a one-vial formulation. With this one-vial formulation, the preparation of the infusion solution is simplified by eliminating the first dilution step.
The two-vial and one-vial formulations contain the same drug substance, docetaxel trihydrate, and the same excipients (ethanol, polysorbate 80 and citric acid).
The one-vial formulation is administered as an aqueous intravenous solution that contains the same drug substance in the same concentration as the currently approved two-vial formulation. The same grade, quality, and quantity of polysorbate 80 are present in the infusion solution of both formulations. The only difference between these two formulations is the quantity of ethanol.

2.2 Quality aspects

Introduction

Docetaxel Winthrop is supplied as a 20 mg/ml pale yellow to brownish-yellow concentrate for solution for infusion. Docetaxel is solubilized in a 50/50 v/v mixture of anhydrous ethanol and polysorbate 80 with citric acid.

Product is contained in a colorless 7 ml type I glass vial closed with grey rubber stopper sealed to the vial by an aluminium cap with a plastic lid.

Docetaxel Winthrop is available in two presentations: 20 mg/1ml and 80 mg/4ml.

Active Substance

The drug substance used in this formulation, docetaxel trihydrate, is identical with the one used in the manufacture of the approved Docetaxel Winthrop 20 mg and 80 mg concentrate and solvent for solution for infusion (EU/1/07/384/001 - 002).

Medicinal Product

- Pharmaceutical Development

The objective of the development was to obtain a one-vial formulation of Docetaxel Winthrop which would simplify preparation of the infusion solution by eliminating the first dilution step and hence the premix solution. The one-vial formulation concentrate is directly diluted with 0.9% sodium chloride solution or 5% glucose solution to prepare the solution for infusion.
The two-vial and one-vial formulations contain the same excipients (ethanol, polysorbate 80 and citric acid) and in the infusion solution the same quantity of polysorbate 80, and the only difference is the quantity of ethanol (2.2-fold higher in the one-vial formulation). Development of the one-vial formulation was conducted with reference to the existing two-vial formulation.

Pharmacokinetic properties of the product were considered during the development of the one-vial formulation. As the pharmacokinetic behaviour was driven by the micelle system and thus was linked to the polysorbate to docetaxel ratio, the formulation of the one-vial was developed so as to keep comparable docetaxel and polysorbate concentrations in the infusion solutions prepared from the one-vial and two-vial concentrates. To confirm that same micelles were obtained in the infusion solutions prepared from the one-vial and the two-vial concentrates, comparative micelles size determinations were conducted and docetaxel solubility was determined in the infusion solution for each formulation. No differences were observed in micelles solubility, formation and size. The same micellar system

was obtained in the infusion solution to be administered to the patient and that pharmacokinetic of the one-vial formulation would consequently be the same as for the two-vial formulation.

It has been demonstrated that the higher level of ethanol in the product will not affect the solubility of docetaxel in the micelles. The MAH also provided an evidence to demonstrate that the higher ethanol content will not affect the release of docetaxel from the micelles upon administration in comparison with the two-vial formulation.

The container-closure system consists of a 7 ml type I glass vial with bromobutyl rubber closure, coated with an ethylene tetrafluoroethylene polymer with aluminium sealing cap. This container-closure system is similar to the one used for the currently marketed two-vial formulation. Chlorobutyl rubber closure of the two-vial formulation has been replaced by a bromobutyl rubber closure for the one-vial formulation as the bromobutyl rubber stopper is better characterized and presents less additives. It presents also good elasticity properties.

- Adventitious Agents

None of the excipients present in the formulation are of animal or human origin. Polysorbate 80 used in the manufacturing process of the medicinal product is of vegetal origin.

- Manufacture of the Product

The manufacturing process adopted for the one-vial formulation is based on the process developed for the existing presentations. As a result the same approach to dispensing, compounding, filtration and filling has been taken. The manufacture of the one-vial product is simpler than that used for the two-vial formulation since there is only the manufacturing process for the concentrate.

The manufacturing process consists of 3 steps: 1) Compounding, 2) Filtration (sterilization) and 3) Vial filling. The compounding process has been designed to ensure that the docetaxel is completely dissolved. In order to ensure that the nominal volume declared on the label can be withdrawn, the vials are filled with an overfill.

The critical steps of the manufacturing process have been identified and adequately studied. Appropriate in-process controls, adequate to control the critical steps of the manufacturing process, have been established.

Manufacturing process validation was performed on three pilot scale primary stability batches and the first validation batches of each strength. Results demonstrated that the compounding process consistently produces a bulk solution which remains homogeneous, throughout the sterile filtration period, and result in a finished product which meets specifications, and that the fill control on the product during the filling process will accurately and reproducibly deliver the required dose.

- Product Specification

The product specification is a standard one for injectable formulations and contains tests with suitable limits for appearance, identification of docetaxel (HPLC and TLC), identification of excipients, clarity and colour, pH, extractable volume, particulate contamination (visible and sub-visible particles), assay (HPLC), water content, alcohol content (GC), related substances (HPLC), sterility and bacterial endotoxins.

The specifications and tests methods proposed for the drug product will adequately control the quality of the product. Analytical methods have been well characterised. Analytical methods not described in the Ph Eur have been validated for the intended use according to ICH guidelines. The HPLC method for assay, identification, and related substances was validated with respect to its specificity, linearity, precision, accuracy, range and robustness. The GC method for determination of ethanol has been validated with respect to its specificity, linearity, accuracy, precision and robustness. The test for sterility has been validated according to Ph Eur (effectiveness of the culture media in the presence and

absence of the product has been studied). The bacterial endotoxin test methods were validated as recommended in the current European Pharmacopoeia.

Results from several batches of both strengths (three primary stability batches and one validation batch) have been presented. Batch analysis results indicate satisfactory uniformity and compliance with the agreed specification.

- Stability of the Product

Stability studies were undertaken under ICH long-term (5°C ± 3°C and 25°C/60% RH), intermediate (30°C/65% RH) and accelerated (40°C/75% RH) conditions. Results were available after 12 months of storage at refrigerated conditions, 18 months of storage at normal and intermediate conditions and after 6 months of storage at accelerated conditions for three primary stability batches and one validation batch. For each condition, vials were stored upright and inverted, in order to assess an eventual product interaction/degradation with the stopper during long term storage.

No new potential degradation products were observed in the one-vial formulation as compared to the two-vial concentrate in stability studies under long-term and accelerated conditions. No significant differences between samples stored upright and those stored inverted were observed.

One batch was subjected to photostability according to ICH recommendations. The photostability testing showed that the drug product could be affected by light. Therefore it is recommended that the storage warning “Protect from light” is applied to all presentations of the one-vial formulation. Similar results were obtained previously for the existing two-vial formulation.

A freeze/thaw cycling study was also conducted. A freeze-thaw study was performed according to the same stability parameters. The results show that the product is not affected by several freeze/thaw cycles. Similar results were obtained previously for the existing two-vial formulation.

Based on the stability data the proposed shelf-life and storage conditions as defined in the SPC are acceptable.

- Comparability Exercise for Drug Product (to be changed in the EPAR to “Medicinal Product”)

Chemical compatibility in polyvinylchloride (PVC) infusion bags containing saline or dextrose solutions and in polyolefin (PO) infusion bags containing saline solution has been performed for the one-vial formulation. No adsorption was observed.
Chemical compatibility has also been demonstrated in Codan giving sets (saline and dextrose solution of docetaxel one-vial - PVC-TOTM (Tri-octyltrimetillate) – DEHP free) and in polypropylene syringes (undiluted docetaxel one-vial).

Obtained results proven similar compatibility behavior with infusion bags and administration sets has been demonstrated of the two-vial and the one-vial formulations.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were minor unresolved quality issues which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measures after the opinion, within an agreed time-frame.

2.3 Non-clinical aspects

In addition to the pharmaceutical data to support the claim of equivalence for the one-vial and two-vial formulations, non-clinical studies (3 toxicology studies and 1 pharmacology study) were also conducted to show the equivalence. Since the two-vial and one-vial formulations contain the same excipients (ethanol, polysorbate 80 and citric acid) and the same quantity of polysorbate 80, and the only difference is the quantity of ethanol (2.2-fold higher in the one-vial formulation), non-clinical studies were conducted on a prototype formulation with higher ethanol content (3.3- fold). This bracketing approach showed that the higher ethanol content of the prototype formulation maintains a similar toxicity profile in mice, similar local tolerance in rabbits, similar *in-vitro* compatibility with human whole blood and plasma and similar anti-tumor activity in B16 melanoma-bearing mice.

The summary of *in-vitro* and *in-vivo* animal studies presented demonstrated equivalence of the existing two-vial formulation to the proposed one-vial formulation.

Environmental risk assessment

No additional studies have been requested and no additional measures for handling and disposal are considered necessary. This new formulation is proposed to facilitate the administration and therefore will be used as an alternative to the existing two vials formulation. As a result, the amount of product used to treat the patients will not be increased. In addition, suppressing the dilution step before the injection of the new formulation reduces the risk of contamination and the quantity of waste to be disposed of.

2.4 Clinical aspects

No new clinical data was submitted for this application since the new one-vial formulation contains the same concentration of docetaxel and the same excipients as the two-vial formulation used in clinical trials. The same grade, quality and quantity of polysorbate 80 is present in the infusion solution of both formulations. The only difference between the two formulations in the infusion bag is the quantity of ethanol increased by approximately 2.2-fold in the one-vial formulation. No differences were observed in micelles solubility, formation and size. It is unlikely that the change to the one-vial formulation will impact docetaxel disposition.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan because the one vial formulation will only substitute the already approved two vials formulation. No additional risk minimisation activities are required beyond those included in the product information.

In addition Docetaxel Winthrop was approved as an informed consent application of Taxotere for which the risk management plan was nor requested and therefore the risk management plan for Docetaxel Winthrop was not deemed necessary.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Pharmacology

The equivalence between two-vial and one-vial formulations has been demonstrated. It is unlikely that the change to the one-vial formulation will impact docetaxel disposition.

Efficacy

No specific clinical study was considered necessary. The efficacy of docetaxel has been assessed previously in the framework of the initial Marketing Authorisation.

Safety

The safety profile of the new one-vial formulation is not expected to be different from the safety profile of the existing formulation. From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

- User consultation

Product information for the one-vial formulation does not have significant changes compared to the 2-vial formulation. Therefore, no additional Readability Testing was performed. The previous results of the Readability Testing showed that the leaflet for Docetaxel Winthrop enabled at least 90% of participants to find, and at least 90% of those to express in their own words, each piece of information tested.

Risk-benefit assessment

The risk/benefit is considered acceptable since the one-vial formulation is introduced to simplify preparation of the infusion solution by eliminating the first dilution step and hence the premix solution.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Docetaxel Winthrop in the treatment of breast cancer (in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer; in combination with doxorubicin for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition; monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent; in combination with trastuzumab for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 and who previously have not received chemotherapy for metastatic disease; in combination with capecitabine for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline), non-small cell lung cancer (for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy; in combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition), prostate cancer (in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer), gastric adenocarcinoma (in combination with cisplatin and 5 fluorouracil for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease) and head and neck cancer (in combination with cisplatin and 5 fluorouracil for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck) was favourable and therefore recommended the granting of the marketing authorisation.