CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Demotaxel Mono 20 mg/ml, concentrate for solution for infusion
Demo SA Pharmaceutical Industry, Greece

docetaxel

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2592/001/DC
Registration number in the Netherlands: RVG 111628

3 June 2013

Pharmacotherapeutic group:	Plant alkaloids and other natural products, taxanes
ATC code:	L01CD02
Route of administration:	intravenous
Therapeutic indication:	see next page
Prescription status:	prescription only
Date of authorisation in NL:	18 March 2013
Concerned Member States:	Decentralised procedure with EL
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Demotaxel Mono 20 mg/ml, concentrate for solution for infusion from Demo SA Pharmaceutical Industry. The date of authorisation was on 18 March 2013 in the Netherlands.

The product is indicated for:

Breast cancer

- Docetaxel in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer and operable node-negative breast cancer. For patients with operable node-negative breast cancer, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer.
- Docetaxel 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 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 in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumours over express HER2 and who previously have not received chemotherapy for metastatic disease.
- Docetaxel 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 is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.
- Docetaxel 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 in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer.

Gastric Adenocarcinoma

- Docetaxel 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 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.

A comprehensive description of the indications and posology is given in the SPC.

Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments.

Docetaxel has been shown *in vitro* to disrupt the microtubular network in cells which is essential for vital mitotic and interphase cellular functions.

Docetaxel was found to be cytotoxic *in vitro* against various murine and human tumour cell lines and against freshly excised human tumour cells in clonogenic assays. Docetaxel achieves high intracellular concentrations with a long cell residence time. In addition, docetaxel was found to be active on some but not all cell lines over expressing the p-glycoprotein which is encoded by the multidrug resistance gene. *In vivo*, docetaxel is schedule independent and has a broad spectrum of experimental antitumour activity against advanced murine and human grafted tumours.

This decentralised procedure concerns a generic application claiming essential similarity with Taxotere concentrate for solution for infusion 20 mg, 80 mg and 160 mg (EU License EU/1/95/001-006) which have been registered through a centralised procedure by Sanofi-Aventis France since 1995.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Demotaxel Mono 20 mg/ml is a product for parenteral use, it is exempted for bioequivalence study (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is docetaxel anhydrous, an established active substance for which a European Pharmacopoeia (Ph.Eur.*) monograph was recently adopted. The active substance is a white to off-white powder, which is soluble in ethanol, methanol, chloroform, dichloromethane and ethyl acetate and insoluble in water. Different polymorphic forms are known, but supporting data of consistent manufacture of the anhydrous form has been provided.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

<u>Manufacturing process</u>

The starting material for the manufacture of docetaxel anhydrous is deemed acceptable. The synthesis has been adequately described and the active substance has been adequately characterized. The starting materials, reagents and solvents and intermediates are controlled adequately.

Quality control of drug substance
The drug substance specification has been established in-house and is based on the Ph.Eur. monograph of docetaxel anhydrous. This is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided. The analytical methods are adequately described and validated.

Stability of drug substance
For one manufacturer, stability data on the active substance have been provided for four production-scale batches stored at 2-8°C (up to 48 months) and 25°C/60%RH (6 months). No clear trends could be observed and all results remain within limits. The claimed retest period of 36 months was accepted with the storage conditions 'store at 5 ± 3°C, protected from light and moisture'.
For the second active substance supplier, stability data on the active substance have been provided for three production-scale batches stored at 25°C/60%RH (12 months) and 40°C/75%RH (6 months). The results demonstrate some trends, but the results remain well within limits after 6 months accelerated and 12 months long-term storage. The retest period of 24 months was granted with the storage condition 'Protected from light, in an airtight container. Store at room temperature'.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Demotaxel Mono 20 mg/ml is a clear pale yellow to brownish-yellow solution. The drug product is packed in clear Ph.Eur. type I 5 ml (1 ml and 4 ml fill) or 10 ml vials (8 ml fill) with a fluorotec plus rubber stopper and an orange or red flip-off aluminium seal. The concentrate is available in presentations of 20 mg/1 ml, 80 mg/4 ml and 160 mg/8 ml docetaxel anhydrous.

The excipients are: polysorbate 80, anhydrous ethanol, anhydrous citric acid.

Pharmaceutical development
The development of the product has been described, the choice and amount of excipients are justified and their functions explained. Compatibility of docetaxel with the excipients has been demonstrated. The formulation and impurity profile of the proposed drug product are similar to the innovator. No bioequivalence studies or clinical trials have been performed. Both the innovator Taxotere and the proposed drug product are micellar formulations which are not considered to be simple aqueous solutions. However, given the facts that the products are the same type of solution, contain the same concentrations of the same active substance and similar excipients, and adequate comparative quality data has been provided, it is agreed that a bioequivalence study can be waived.
The development of the manufacturing process, the choice of container closure system and microbiological attributes have been adequately discussed. No active substance overage is applied in the formulation. The choice of sterilization by filtration and aseptic processing was sufficiently justified. The pharmaceutical development of the product has been adequately performed and pharmaceutical equivalence with the innovator has been adequately demonstrated.

Microbiological attributes
Microbiological attributes are controlled through sterility and bacterial endotoxin testing (calculated limit as per Ph.Eur.) and is ensured by container closure integrity testing (leak test).

Manufacturing process
The drug product is manufactured by preparation of the bulk solution, aseptic filtration, filling, stoppering, sealing, inspection and packaging. The bulk solution is prepared by mixing of the excipients, followed by

mixing with docetaxel. The manufacturing process has been adequately validated for the proposed commercial batch sizes.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The drug product specification includes tests for appearance, identification, color and clarity of solution, pH, extractable volume, particulate matter (sub-visible particles), ethanol content, related substances, assay, sterility and bacterial endotoxins. The release and shelf-life specifications are identical, except for limits for related substances. The drug product specifications are acceptable. Limits for related substances have been tightened to qualified limits. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on four batches of each fill, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided twelve production scaled batches stored at 25°C/60%RH (18 months), 30°C/75%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in clear Ph.Eur. type I vials with a fluorotec rubber stopper and an orange or red flip-off aluminium seal.
Based on observed trends under accelerated storage conditions, it can be concluded that the drug product shows temperature dependent degradation. In addition, the product was shown to be photosensitive. Following the decision tree in Appendix A to the NfG on Evaluation of Stability Data (ICH Q1E), a maximum extrapolation of 6 months can be applied, resulting in a shelf-life of 24 months. The storage condition “Do not store above 25°C. Store in the original package in order to protect from light” is acceptable in view of the stability data and the storage condition of the reference product.

In-use stability
Stability of the diluted solution (with 5% dextrose and 0.9% NaCl) has been demonstrated at 25°C (24 hours) and 2-8°C (7 days). A dilution study was carried out with a batch approaching the end of shelf life, using 0.9% sodium chloride injection (0.3 mg/ml and 0.74 mg/ml), (initial/4/6/2/48 hours and 7 days). Results remained well within the acceptance criteria.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Taxotere which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of docetaxel released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Docetaxel is a well-known active substance with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

Demotaxel Mono 20 mg/ml, concentrate for solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Demotaxel Mono 20 mg/ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk management plan

Docetaxel was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of docetaxel anhydrous can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Taxotere.

Readability test

The package leaflet has not been evaluated via a user consultation study. A bridging report was provided to refer to an earlier tested PL for another docetaxel generic. The bridging report focuses mainly on the lay-out of the two PLs. Considering that the PL is fully in line with the innovator’s PL, bridging is acceptable. A separate user test is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Demotaxel Mono 20 mg/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic forms of Taxotere concentrate for solution for infusion 20 mg/1 ml, 80 mg/4 ml and 160 mg/8 ml. The reference product Taxotere is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Demotaxel Mono 20 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 29 January 2013. Demotaxel Mono 20 mg/ml, concentrate for solution for infusion was authorised in the Netherlands on 18 March 2013.

The date for the first renewal will be: 29 January 2018.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached