



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 November 2011
EMA/40836/2012

Assessment report

Docetaxel Mylan

International non-proprietary name: **docetaxel**

Procedure No. **EMA/H/C/002317**

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

Medicinal product no longer authorised



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Medicinal product no longer authorised

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan S.A.S. submitted on 12 August 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Docetaxel Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– ‘Generic of a Centrally authorised product’. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP 21 April 2010.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer

The legal basis for this application refers to:

A - Centralised / Article 10(1) / Generic application.

The application submitted is composed of administrative information and complete quality data instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

Product name, strength, pharmaceutical form: Taxotere 20 mg/0.5 ml and 80 mg/2 ml concentrate and solvent for solution for infusion Taxotere 80 mg/2 ml, concentrate and solvent for solution for infusion, Taxotere 20 mg/1 ml concentrate for solution for infusion, Taxotere 80 mg/4 ml concentrate for solution for infusion, Taxotere 160 mg/8 ml concentrate for solution for infusion

Marketing authorisation holder: Aventis Pharma S.A., France

Date of authorisation: 27 November 1995

Marketing authorisation granted by: Community

Community Marketing authorisation number: EU/1/95/002/001 - 002

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

Product name, strength, pharmaceutical form: Taxotere 20 mg/1 ml concentrate for solution for infusion, Taxotere 80 mg/4 ml concentrate for solution for infusion, Taxotere 160 mg/8 ml concentrate for solution for infusion

Marketing authorisation holder: Aventis Pharma S.A., France

Date of authorisation: 27 November 1995

- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/95/002/003 - 005

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

An inspection of the manufacturing site responsible for the manufacture of the finished products was carried out by the Competent Authorities of France [The French Agency for the Safety of Health Products]. The findings of the inspection are in compliance with the EU Good Manufacturing Practice requirements.

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Pierre Demolis.

- The application was received by the EMA on 12 August 2010.
- The procedure started on 18 August 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 November 2010.
- During the meeting on 13-16 November 2010, 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 16 December 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 March 2011.
- The summary report of the GMP inspection carried out at the site responsible for the manufacture of the finished products between 16 August 2011 and 19 August 2011 was issued on 29 September 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 6 May 2011.
- During the CHMP meeting on 16-19 May 2011, 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 consolidated List of Outstanding Issues on 17 June 2011.
- During the CHMP meeting on 20-23 June 2011 the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated 2nd List of Outstanding Issues on 12 October 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 2 November 2011.
- During the meeting on 14-17 November 2011, 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 Mylan on 17 November 2011.

2. Scientific discussion

2.1. Introduction

Docetaxel Mylan concentrate for solution for infusion is a generic medicinal product containing the active substance docetaxel. The reference medicinal product is Taxotere concentrate for solution for infusion authorised 27 November 1995.

Docetaxel is an antineoplastic agent that acts by promoting the assembly of tubulin into stable microtubules and inhibits their assembly, which leads to a decrease of free tubulin and to cancer death.

The safety and efficacy profile of docetaxel for the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer has been demonstrated in several clinical trials for the reference medicinal product. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this active substance.

The indications for Docetaxel Mylan are as follows:

Breast cancer

Docetaxel Mylan in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with:

- operable node-positive breast cancer
- 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 (see section 5.1).

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

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

Gastric adenocarcinoma

Docetaxel Mylan 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 Mylan 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.

2.2. Quality aspects

2.2.1. Introduction

Docetaxel Mylan is a sterile concentrate for solution for infusion at 20 mg/ml, available in three presentations: 1ml, 4ml and 10ml corresponding to 20mg, 80mg and 200mg of anhydrous docetaxel. The concentrate is to be diluted with 0.9 % sodium chloride solution or 5 % glucose solution prior to infusion.

The excipients used in the formulation are polysorbate 80, citric acid and ethanol.

The formulation of this product is similar to the reference product Taxotere.

2.2.2. Active substance

Docetaxel is an efficient inhibitor of eukaryotic cell replication, blocking cells in the late G2-M phase of the cell cycle. It promotes abnormal assembly of microtubules via stabilization. Docetaxel INN is N-Debenzoyl-N-(tert-butoxycarbonyl)-10-deacetyltaxol; $C_{43}H_{53}NO_{14}$ = 807.88.

Docetaxel is a white to off-white crystalline powder freely soluble in anhydrous ethanol, soluble in 95% ethanol, acetone and methanol, sparingly soluble in chloroform and insoluble in water. Docetaxel anhydrous is considered hygroscopic and it is optically active. A polymorphic study demonstrates that the crystalline form of docetaxel anhydrous produced is consistent from batch to batch. Particle size

has been determined on three batches showing similar sizes therefore this parameter is not included in the specification.

Docetaxel possesses 11 asymmetric carbon atoms, resulting in a considerable number of potential stereoisomers. Only one isomer as given in the chemical name is defined as the drug substance. This configuration is the one that appears in natural taxanes as paclitaxel. One other diastereoisomer, i.e. 7-epidocetaxel, is a potential synthesis but also degradation impurity.

Manufacture

Docetaxel is manufactured by two different manufacturers and the Active Substance Master File (ASMF) procedure was followed for both manufacturers. The route of synthesis differs for the two sites. The route of synthesis was briefly described in the open part but the detailed information was provided in the restricted part of the ASMF. The process was acceptably described for both manufacturing sites.

The structure has been confirmed by elemental analysis, UV, IR, ¹³C and ¹H NMR and MS data.

The elemental analysis data is similar between the experimental and theoretical values. The ¹³C and ¹H NMR data are in accordance with data reported in the literature. A low resolution as well as high resolution mass spectroscopy has been performed. A polymorphic study by IR, DSC, XRPD and electron microscopy on three batches confirmed that consistently the same polymorph was formed.

Impurities are well controlled in the active substance and limits are in line with ICH Q3A and ICH Q3C guidelines.

Specification

Specification is in agreement with the new monograph for docetaxel trihydrate, with relevant modifications regarding the anhydrous state.

The specification include test for appearance (visual inspection), appearance of solution (visual inspection), identification (HPLC, IR), water (Karl Fisher) specific rotation (Ph. Eur.), heavy metals (Ph. Eur.), residue on ignition (Ph. Eur.) assay (Ph. Eur.), related substances (Ph. Eur.), total aerobic microbial count (Ph. Eur.) and residual solvents (Ph. Eur.).

Impurities have been evaluated and found to be acceptable from the point of view of safety.

The analytical methods are essentially the same in both manufacturing sites and are suitable to control the quality of the active substance. The methods have been well described and validated according to ICH Q2 (R1).

Batch analysis results on 7 and 4 batches for each site have been submitted. The results comply with the specifications and therefore confirm consistency and uniformity of the manufacturing processes.

Stability

The active substance is either packed in double LDPE bags, sealed with twist ties, placed in PE or HDPE bottles with caps or packed in high-density polyethylene bottle and a HDPP cap and sealed with cold shrink self-fusing tape, depending of the manufacturing site used for the production of the active substance. Specifications for the packaging material have been provided and are in compliance with Ph. Eur 3.2.2 and EU Directives 2004/19/EC and 2002/72/EC.

The storage conditions differ in the two manufacturing sites and therefore the stability studies were performed under different conditions. A total of 4 batches were stored in line with ICH conditions for

substances intended to be stored under refrigeration, i.e. long term conditions ($5 \pm 3 \text{ }^\circ\text{C}$) and accelerated conditions ($25 \pm 2 \text{ }^\circ\text{C}/60 \pm 5 \text{ \% RH}$). At the alternative manufacturing site, the stability studies were performed according to ICH at $25^\circ\text{C}/60\% \text{ RH}$ (long term conditions), $30^\circ\text{C}/65\% \text{ RH}$ (intermediate conditions) and $40^\circ\text{C}/75\% \text{ RH}$ (accelerated conditions).

The parameters tested included appearance, identification, assay, purity, specific rotation, microbial purity and water content. The stability data supports the retest period.

2.2.3. Finished medicinal product

The proposed drug product is a concentrate for solution for infusion at 20 mg/ml, available in three presentations: 1ml, 4ml and 10ml corresponding to 20mg, 80mg and 200mg of anhydrous docetaxel. The concentrate is to be diluted before infusion. The proposed medicinal product is intended for dilution in 0.9 % sodium chloride or 5% glucose to produce a final concentration of 0.3 to 0.74 mg/ml in the infusion solution.

The concentrate for solution for infusion is a clear and yellowish solution. The drug product comprises the following excipients: polysorbate 80, citric acid anhydrous and ethanol anhydrous.

The container closure system consists of a colourless type I glass vial with a 20 mm fluorinated polymer coated bromobutyl rubber stopper and aluminium crimp with plastic cap. Nominal capacity of the vial is 6ml for the 20mg strength, 10ml for the 80mg strength and 15ml for the 200mg strength.

Pharmaceutical development

Development of the drug product is based on the formulation, dosage form, concentration and use of the reference product Taxotere.

Taxotere is presented as a concentrate for solution for infusion, available in three dosages of docetaxel trihydrate corresponding to 20 mg, 80 mg and 160 mg per vial of anhydrous docetaxel in a solution of ethanol/polysorbate 80 (50/50). The composition of the solution is homothetic for all strengths (20 mg/ml).

The drug product is presented as a concentrate for solution for infusion, available in three dosages corresponding to 20 mg, 80 mg and 200 mg per vial of anhydrous docetaxel. The composition of the solution is homothetic for all three strengths (20 mg/ml). The addition of the 200 mg presentation corresponds to a potential hospital need, in relation to the highest posology.

The concentration of polysorbate 80 in the drug product was set at the same level as in Taxotere. Different formulations were tested after storage in accelerated conditions (40°C and 60°C) during 4 weeks. The formulation consisting in anhydrous docetaxel dissolved in a mixture of ethanol/polysorbate 80 (50:50) was selected considering both chemical and physical stabilities.

The composition of the generic formulation is qualitatively identical to the innovator product. Taxotere formulation contains a specific grade of polysorbate 80 which already includes in its composition citric acid. The amounts of surfactant are nearly identical between the two products. The target pH value in the drug product (concentrate) is the same for the generic and the innovator, indicating that the amount of citric acid necessary to adjust pH is similar. The amount of ethanol is the same for both formulations.

The intravenous medicinal product is intended for administration by slow infusion. The active substance is insoluble in water and solubilisation is achieved by adding a surfactant to the formulation, i.e. polysorbate 80. At the levels which occur in the concentrate and in infusion solutions, Polysorbate 80 forms micelles which solubilise the docetaxel and precipitation of the drug in aqueous solution does not

occur. Considering the micellar nature of the product, it was important to characterise the micelle solution and compare it to the reference product prior to administration, i.e., in the infusion bag. The characterisation of the micelle solution included the determination of the pH, micelle size and micelle size distribution. In addition, comparative docetaxel in vitro release data from micelles prior to administration and once the infusion started in human plasma was also performed. The results of the studies showed the similarity of both products with regards to micellar characteristics. Considering these comparable in vitro results and the similarity of this generic formulation to the formulation of the reference product, it was considered that taken together, these findings could be used to support a biowaiver for this 'complex' injectable.

Adventitious agents

None of the excipients used in the formulation of docetaxel concentrate for solution for infusion are of animal origin.

Manufacture of the product

Manufacturing process of Docetaxel 20mg/ml concentrate for solution for infusion is classified as non-standard. The manufacturing process comprises preparation of the solution followed by double sterile filtration, filling of the solution into sterile vials, stoppering and sealing. The drug product is aseptically manufactured as it is not stable at high temperature to allow final sterilization.

There are several in-process controls such as the determination of the bioburden prior to filtration, determination of the pH prior to filling, testing of the integrity of the sterilising filter before and after filtration and check of fill weight at regular intervals throughout the filling operation.

The manufacturing process validation has been performed using four production scale batches from one source of API. Therefore, the Committee recommends confirmation of the process validation of the finished product with the first batch manufactured with the second source of API. This request is included in the list of recommendations.

Product specification

The specifications for Docetaxel Mylan 20 mg/ml concentrate for solution for infusion include tests for: appearance of solution (visual examination) identification of docetaxel (HPLC, GC retention time and UV absorption), identification of ethanol (GC retention time), identification of polysorbate 80 (Ph. Eur.), identification of citric acid (Ph. Eur.), assay of docetaxel (HPLC), assay of ethanol (GC) related substances (HPLC), sealing test, extractable volume, particulate contamination (subvisible particles), pH, sterility and bacterial endotoxins. The analytical methods were well described and validated in agreement with ICH guidelines. For the analytical methods described in the Ph. Eur validation was deemed to be unnecessary.

The routine specifications and tests methods proposed for the drug product adequately control the quality of the product.

Batch results were provided for four batches of the finished product. The results were to be in compliance with the proposed specification.

Stability of the product

Stability studies were performed under ICH long-term, intermediate and accelerated conditions (i.e. 5°C ± 3°C, 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH). Stability studies were performed on six primary stability batches of the finished product. The tests performed were appearance, colour, compounds identifications, docetaxel assay and related impurities, ethanol content, pH, extractable volume, particulate contamination, endotoxins, sterility, sealing test.

Compatibility with infusion solvents and respective storage instructions were adequately addressed. Diluted product at the extremes of the range of concentrations likely to be used in clinical practice has been studied. Effect of temperature on stability of these complex systems has been evaluated. An infusion simulation study was performed according to the instructions of the SmPC (recommended solvents, non-PVC bags, and extreme infusion solutions concentrations, one-hour infusion duration) in order to demonstrate stability of the micellar component upon administration. The Applicant has committed to perform an in-use stability study using batches at end of shelf life. It will allow confirming the proposed storage conditions of the diluted solution. A recommendation has been included in the list of recommendations.

Stability data have been provided in order to support a 1-year shelf-life period with a special precaution for storage, i.e. do not store at a temperature above 25 °C.

In summary, the stability results support the shelf-life and storage conditions as defined in the SmPC.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The active substance and finished product have been adequately described. The finished product is manufactured using a non-standard process. Sufficient validation data has been provided to assure that the process is robust and well controlled and produces a uniform product. The medicinal product consists of a micellar solution, i.e., the active substance is solubilised in surfactant micelles. The composition of the generic formulation is qualitatively identical and quantitatively practically identical to the innovator product Taxotere concentrate for solution for infusion. Development of the generic product was based on the formulation, dosage form, concentration and use of the reference product Taxotere. No bioequivalence study has been submitted by the applicant to demonstrate the pharmaceutical equivalence of their product to the originator. Comparative experimental data regarding the physicochemical parameters and impurity profile before and after dilution in the two solvents recommended in the SmPC and in particular, mean size, size distribution and stability of the micelles that are formed in the final solution before intravenous administration, according to the guidelines of the SmPC, have been compared. Moreover, comparative docetaxel in vitro release data from micelles prior to administration and once the infusion started in human plasma was also performed. No significant difference was observed from the comparative studies between the generic product and the reference product.

Therefore, similarity between Docetaxel Mylan and the reference product Taxotere can be accepted and no additional human bioequivalence study was considered necessary in this particular case.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The CHMP recommends confirmation of the process validation of the finished product with the first batch manufactured with the second source of API.
2. The CHMP recommends confirmation of the shelf life of the finished product with an in-use stability study performed with batches at the end of shelf life.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Docetaxel Mylan manufactured by Mylan S.A.S. is considered unlikely to result in any significant increase in the combined sales volumes for all docetaxel containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.4. Clinical aspects

2.4.1. Introduction

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of docetaxel based on published literature. The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product.

Exemption

As Docetaxel Mylan is administered as an aqueous solution for infusion, no comparative dissolution data have been generated. However, given that the drug substance is not very soluble and that a tensioactive agent is used for solubilising the drug substance as micelles in the solution / infusion solution, the applicant has performed a comparative study of the release of docetaxel from micelles,

between both formulations (Taxotere and Docetaxel Mylan). Free fraction of [3H]-docetaxel was determined using one equilibrium dialysis system in 0.9% sodium chloride solution and in human plasma. The results confirmed that release profiles of Docetaxel Mylan and Taxotere are comparable (see Quality section).

Therefore, similarity between Docetaxel Mylan and the reference product Taxotere can be accepted and no additional human bioequivalence study was considered necessary in this particular case.

2.4.2. Pharmacokinetics

No new pharmacokinetic studies were presented and no such studies are required for this application.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Docetaxel Mylan was provided and was accepted by the CHMP. The summary of literature referred to the proposed indications:

Breast cancer

Docetaxel Mylan in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with:

- operable node-positive breast cancer
- 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 (see section 5.1).

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

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

Gastric adenocarcinoma

Docetaxel Mylan 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 Mylan 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.

This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

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 applicant to submit a risk management plan because the active substance docetaxel has been in use for many years, and has a well-established safety profile. Routine pharmacovigilance activities in accordance with EU regulations will be undertaken whilst the product is authorised, including review of individual case safety reports, literature review, signal detection procedures and generation of the required safety reports. Specific additional risk minimisation activities are not envisaged as the safety profile of the medicinal product is well-established.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

PSUR submission

The PSUR submission schedule should follow the PSUR schedule for the reference product, which currently is on a 3-yearly cycle. The next data lock point for the reference medicinal product is 30 November 2013.

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of docetaxel concentrate for solution for infusion. The reference product Taxotere is indicated for the treatment of breast cancer, non-small lung cancer, prostate cancer, gastric adenocarcinoma, head and neck cancer. No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

As Docetaxel Mylan is administered as an aqueous solution for infusion, no comparative dissolution data have been generated. However, given that the drug substance is not very soluble and that a surfactant is used for solubilising the drug substance as micelles in the solution / infusion solution, the applicant has performed a comparative study of the release of docetaxel from micelles, between both formulations (Taxotere and Docetaxel Mylan). Free fraction of [³H]-docetaxel was determined using one equilibrium dialysis system in 0.9% sodium chloride solution and in human plasma. The results confirmed that release profiles of Docetaxel Mylan and Taxotere are comparable.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Docetaxel Mylan in the treatment of breast cancer, non-small lung cancer, prostate cancer, gastric adenocarcinoma, head and neck cancer is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk management system

Not applicable

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product.

Medicinal product no longer authorised