



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

15 March 2012  
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Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

### **Docetaxel Accord**

International non-proprietary name: **docetaxel**

Procedure No. **EMA/H/C/002539**

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



## Table of contents

<b>Background information on the procedure .....</b>	<b>4</b>
1.1. Submission of the dossier.....	4
Information on paediatric requirements .....	4
Licensing status .....	4
1.2. Steps taken for the assessment of the product .....	5
<b>2. Scientific discussion .....</b>	<b>5</b>
2.1. Introduction .....	5
2.2. Quality aspects .....	7
2.2.1. Introduction .....	7
2.2.2. Finished medicinal product.....	8
2.2.3. Discussion on chemical, and pharmaceutical aspects .....	10
2.2.4. Conclusions on the chemical, pharmaceutical and biological aspects .....	10
2.3. Non- clinical aspects.....	10
2.3.1. Introduction .....	10
2.3.2. Ecotoxicity/Environmental risk assessment.....	11
2.4. Clinical aspects .....	11
2.4.1. Introduction .....	11
2.4.2. Pharmacokinetics .....	11
2.4.3. Pharmacodynamics.....	11
2.4.4. Post marketing experience.....	11
2.4.5. Conclusions on clinical aspects .....	12
2.5. Pharmacovigilance.....	13
<b>3. Benefit-risk balance .....</b>	<b>13</b>
<b>4. Recommendation .....</b>	<b>14</b>

## **List of abbreviations**

ASMF: Active Substance Master File

CHMP: Committee for Medicinal Products for Human Use

EMA: European medicines agency

GCP: Good Clinical Practice

ERA: Environmental Risk Assessment

MA: Marketing Authorisation

MAH: Marketing authorisation holder

SmPC: Summary of product characteristics

# Background information on the procedure

## 1.1. Submission of the dossier

The applicant Accord Healthcare Ltd. submitted on 31 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Docetaxel Accord, 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 on 26 April 2011.

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, head and neck cancer.

### **The legal basis for this application refers to:**

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data instead of non-clinical and clinical data 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/0.5ml, 80 mg/2ml, concentrate and solvent for solution for infusion
  - Marketing authorisation holder: Aventis Pharma S.A.
  - 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/1ml, 80 mg/2ml and 160 mg/8ml, concentrate for solution for infusion
  - Marketing authorisation holder: Aventis Pharma S.A.
  - Date of authorisation: 27 November 1995
  - Marketing authorisation granted by:
    - Community
  - Community Marketing authorisation number: EU/1/95/002/003-005

### **Licensing status**

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

## ***1.2. Steps taken for the assessment of the product***

The Rapporteur appointed by the CHMP was:

Rapporteur: Tomas Salmonson

- The application was received by the EMA on 31 May 2011.
- The procedure started on 22 June 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 09 September 2011.
- During the meeting on 17-20 October 2011, 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 October 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 November 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 December 2011.
- During the CHMP meeting on 16-19 January 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 13 February 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 February 2012.
- During the meeting on 12-15 March 2012, 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 Accord on 15 March 2012.

## **2. Scientific discussion**

### ***2.1. Introduction***

Docetaxel Accord concentrate for solution for infusion is a generic medicinal product containing the active substance docetaxel. The reference medicinal product is Taxotere concentrate and solvent for solution for infusion authorised on 27 November 1995. The active substance of the reference product is docetaxel.

Docetaxel is an antineoplastic agent which binds to free tubulin, promotes the assembly of tubulin into stable microtubules and inhibits their depolymerisation/disassembly. Docetaxel disrupts the microtubular network in cells, which is essential for vital mitotic and interphase cellular functions.

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, details of which can be found in the EPAR of 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 proposed for Docetaxel Accord are identical to the indications for the reference medicinal product Taxotere and are as follows:

#### Breast cancer

Docetaxel Accord 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 SmPC section 5.1).

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

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

#### Gastric adenocarcinoma

Docetaxel Accord 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 Accord 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 Accord is presented as a sterile, clear pale yellow to brownish 20 mg/ml solution, available in three presentations: 1ml, 4ml and 8 ml. Nominal capacity of the vial is 5ml for the 1 and 4 ml presentations, and 10 ml for the 8 ml presentation.

The concentrate is to be further diluted prior to infusion with either a 5% glucose solution or a 0.9% sodium chloride solution to achieve a final concentration of 0.74 mg/ml.

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

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

### **Active substance**

The active substance is docetaxel, a well known active substance described in the Ph.Eur. Its chemical name is 1,7 $\beta$ ,10 $\beta$ -Trihydroxy-9-oxo-5 $\beta$ ,20-epoxytax-11-ene-2 $\alpha$ ,4,13 $\alpha$ -triyl 4-acetate 2-benzoate 13-[(2R,3S)-3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate].

It is synthesized in the anhydrous form. It is a white to off-white crystalline powder, practically insoluble in water; freely soluble in anhydrous ethanol and tetrahydrofuran; and soluble in methylene chloride, methanol, acetone and ethylacetate. Its partition coefficient (log P) is 4.26.

Docetaxel anhydrous has eleven chiral centres resulting in a considerable number of potential stereoisomers. Only one isomer as given in the chemical name is defined as the drug substance.

The chemical structure of the molecule has been established by spectral (UV, IR, 1H and 13C NMR and MS) and elemental analysis.

The active substance exhibits polymorphism. XRD results confirm that the same crystalline form is consistently obtained by both manufacturers.

### **Manufacture**

Docetaxel is manufactured by two different manufacturers. The Active Substance Master File (ASMF) procedure was followed by both of them.

The manufacturing processes have been adequately described and satisfactory specifications have been set for reagents, solvents and auxiliary materials used in the process. All critical in-process controls parameters have been well established and justified.

The analytical methods have been well described and validated according to ICH Q2 (R1).

One of the manufacturers packs docetaxel active substance into transparent PE bags which are tied with strip seal and placed in a poly bag tied with a strip seal. These bags are further placed in a black PE bag with strip seal and a desiccant between the black bag and the poly bag. The bags are stored in HDPE drums.

The other manufacturer packs the active substance in double LDPE bags sealed with twist ties, which are further placed into PE bottles together with a desiccant.

Both manufacturers have provided specifications for the bags and have confirmed that the material in contact with the drug substance is compliant with 2002/72/EC and Ph. Eur. 3.2.2.

### ***Specification***

The specification of docetaxel was set to be in line with the current Ph.Eur. monograph and relevant ICH guidelines. The active substance specification includes tests for appearance, appearance of solution, solubility, identification (FT-IR, HPLC), specific optical rotation, water content (Karl Fisher), assay (HPLC), related substances (HPLC), residual solvents (GC), heavy metals, sulphated ash, bacterial endotoxins and microbial limit test.

A discussion on potential impurities arising from the starting material, the reagents, the route of synthesis or degradation has been provided. It includes organic impurities, inorganic impurities and residual solvents. All the impurities are controlled in the final active substance specification in accordance with the Ph.Eur. requirements and ICH Q3A and ICH Q3C guidelines. The impurity limits are acceptable and there is no concern from the point of view of safety.

The absence of a test for polymorphism in the drug substance specification is justified based on batch analysis data (X-ray diffraction) and stability studies conducted on docetaxel anhydrous produced by both manufacturers. These studies have confirmed that polymorphic form A is consistently produced by the submitted manufacturing processes and is considered as a stable polymorph when protected from moisture.

Batch analysis data from a minimum of three production scale batches from each manufacturer have been provided. The results confirm batch-to-batch consistency and compliance with the Ph. Eur. monograph and the additional specification.

### ***Stability***

Data from stability studies on a minimum of three production scale batches have been provided. Samples were stored for up to 12 months (one manufacturer) or 48 months (the other manufacturer) under long term conditions and for 6 months under accelerated conditions in accordance with ICH requirements. All batches have been tested for conformance with the specification using stability indicating analytical methods. In all cases the batch analysis data met the predefined specification and no significant changes were observed.

In addition stability data have been provided under stress conditions (heat, acid hydrolysis, base hydrolysis, photo degradation, water hydrolysis and hydrogen peroxide treatment).

The proposed retest periods by each active substance manufacturer are supported by the stability results provided.

### **2.2.2. Finished medicinal product**

Docetaxel Accord 20 mg/ml concentrate for solution for infusion is a sterile, clear pale yellow to brownish solution. The product is available in 1 ml, 2 ml and 4 ml clear glass vials presented with a flurotec plus rubber stopper and flip-off seal. The flip-off cap is orange for the 1 ml presentation and red for the 4ml and 8 ml presentations.

### ***Pharmaceutical development***

The pharmaceutical development was aimed at developing a stable injectable solution similar to Taxotere single vial of 20 mg/ml concentrate for solution for infusion.



The formulation of Docetaxel Accord is qualitatively similar to that of the innovator product Taxotere. The excipients used in the formulation are polysorbate 80, citric acid anhydrous and ethanol anhydrous. Anhydrous Citric Acid is used as antioxidant and pH adjusting agent, polysorbate 80 as a solubilizer, and anhydrous ethanol as a solvent. All the excipients employed are widely used in parenteral dosage forms and comply with the Ph. Eur.

The active substance is insoluble in water and solubilisation is achieved by adding a surfactant, polysorbate 80, to the formulation. At the levels which occur in the concentrate and in infusion solutions, polysorbate 80 forms micelles which solubilise 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 micelle size distribution, critical micelle concentration, osmolality and in vitro release of docetaxel from the micellar solution prior to administration.

The results of these studies have shown 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 is considered that taken together, these findings can be used to support a biowaiver for this 'complex' injectable.

### ***Adventitious agents***

None of the excipients used in the formulation of Docetaxel Accord concentrate for solution for infusion are of animal or human origin.

### ***Manufacture of the product***

The manufacturing process has been sufficiently described. It comprises four main steps: formulation of the bulk solution, double sterile filtration (0.22 µm), aseptic 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.

Several studies have been conducted to optimise the manufacturing process i.e. evaluation of the order of the addition of the excipients, optimisation of excipient concentration, selection of inert gas and bulk holding times.

Several in-process controls such as the determination of the clarity of the citric acid and polysorbate 80 solution, pH of the bulk solution, bioburden and filter integrity testing prior to filtration, check of fill weight and bacterial endotoxin in the vials have been identified.

Batch analysis data on twelve batches (four of each presentation) have confirmed that the defined process reliably produces a product which meets the proposed release specification.

### ***Product specification***

The specification for Docetaxel Accord 20 mg/ml concentrate for solution for infusion include tests for: description, identification (TLC and HPLC), pH, extractable volume, particulate contamination (subvisible particles), sterility, assay (HPLC), related substances (HPLC), bacterial endotoxins, ethanol content, colour of solution, and clarity of solution.

The non-compendial analytical methods have been well described and validated in agreement with ICH guidelines.

## ***Stability of the product***

Stability studies have been performed under long-term (25°C /60%RH, 15 months), intermediate (30°C/65% RH, 12 months) and accelerated (40°C /75%RH, 6 months) ICH conditions. Stability studies have been performed on four primary stability batches of the finished product. The tests performed were description, pH, particulate contamination (sub visible), sterility, bacterial endotoxins, assay, related substances, ethanol content, color of solution and clarity of solution.

Based on the stability data provided, the proposed shelf life and storage conditions as defined in the SmPC are acceptable.

### **2.2.3. 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. The composition of the generic formulation is qualitatively identical and quantitatively nearly 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 reference medicinal product. Comparative experimental data regarding the physicochemical characteristics (e.g. micelle size distribution, critical micellar concentration, in vitro release of docetaxel from the micellar solution) in the product ready to use (after dilution with 0.9% sodium chloride or 5% glucose) and impurity profile have been provided. No significant difference was observed from the comparative studies between the generic product and the reference product.

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

### **2.2.4. 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 SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

## ***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 Accord manufactured by Accord Healthcare Ltd. 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***

No bioequivalence studies have been conducted. The Applicant outlined that Docetaxel Accord is a micelle solution for intravenous administration and, according to the Guideline on the investigation of Bioequivalence (CPMP/QWP/EWP/1401/98/Rev 1), micelle formulations may be eligible for biowaiver if rapid disassembly of the micelle on dilution occurs, the method and rate of administration is the same as the reference medicinal product and the excipients do not affect the disposition of the drug substance.

As Docetaxel Accord 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 Accord). Free fraction of [3H]-docetaxel was determined using one equilibrium dialysis system in 5% glucose solution at initial and after 7 days when stored in a refrigerator. The results confirmed that release profiles of Docetaxel Accord and Taxotere are comparable (see Quality section).

Therefore, 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 Accord was provided and was accepted by the CHMP. The summary of literature referred to the proposed indications:

### Breast cancer

Docetaxel Accord 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 SmPC section 5.1).

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

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

### Gastric adenocarcinoma

Docetaxel Accord 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 Accord 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. The application is based on a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified.

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.

### ***User consultation***

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Docetaxel 20 and 80 mg concentrate and solvent for solution for infusion approved through a decentralized procedure. Moreover, the proposed package leaflet (PL) of Docetaxel Accord 20 mg/ml concentrate for solution for infusion is same as the PL of the reference medicinal product Taxotere concentrate for solution for infusion.

The bridging report submitted by the applicant has been found acceptable.

## **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 nonclinical 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 Accord 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 Accord). Free fraction of [<sup>3</sup>H]-docetaxel was determined using one equilibrium dialysis system in 5% glucose solution at initial and after 7 days when stored in a refrigerator. The results confirmed that release profiles of Docetaxel Accord 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 Accord 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.

### ***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

Not applicable