15 March 2012
EMA/305675/2012

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Docetaxel Kabi

International non-proprietary name: **docetaxel**

Procedure No. **EMEA/H/C/002325**

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

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List of abbreviations

GC: Gas chromatography

HPLC: High-performance liquid chromatography

IR: Infrared spectroscopy

LDPE: Low-density polyethylene

XRD: X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Fresenius Kabi Oncology Plc submitted on 31 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Docetaxel Kabi, 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 May 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, 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 and complete quality data with the reference medicinal product Taxotere 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 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 - 005

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

Product name, strength, and 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. 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 31 May 2011.
- The procedure started on 22 June 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 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 21 October 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 30 November 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 January 2012.
- During the CHMP meeting on 13-16 February 2012, 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 22 February 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 8 March 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 Kabi on 15 March 2012.

2. Scientific discussion

2.1. Introduction

Docetaxel Kabi 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 on 27 November 1995.

Docetaxel is an antineoplastic agent that acts by promoting the assembly of tubulin into stable microtubulues 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 Kabi are identical to the indications of Taxotere and are as follows:

Breast cancer

Docetaxel Kabi 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.

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

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

Gastric adenocarcinoma

Docetaxel Kabi 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 Kabi 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 KABI is a clear, colourless to pale yellow solution, supplied in vials as a sterile concentrate for solution for infusion at 20 mg/ml, available in four presentations: 4 ml, 6 ml, 8 ml and 9 ml corresponding to 80 mg, 120 mg, 160 mg and 180 mg 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, anhydrous citric acid and ethanol anhydrous.

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.

Docetaxel anhydrous is a white or almost white crystalline powder practically insoluble in water, freely soluble in anhydrous ethanol, soluble in methylene chloride. Docetaxel anhydrous is considered hygroscopic and it is optically active.

The docetaxel molecule can be divided into two parts; the side chain and the taxol skeleton. The side chain of docetaxel contains two chiral centres (2R, 3S). Taxol skeleton consists of three fused rings with nine chiral centres, two six-membered rings and an eight-membered ring and peripheral functionality.

Docetaxel exhibits polymorphism consisting of single crystalline morphological form with yielding consistent IR spectra and XRD patterns in three validation batches.

Manufacture

Docetaxel is manufactured by a single manufacturer and the Active Substance Master File (ASMF) procedure was followed for this site. 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 in the ASMF.

Specification

The specification for docetaxel includes tests for appearance (visual inspection), appearance of solution (visual inspection), solubility (visual inspection), identification (IR), identification (specific optical rotation), water (Ph. Eur), heavy metals (visual inspection), sulphated ash , assay (HPLC), related substances (HPLC), total aerobic microbial count, bacterial endotoxins (Ph. Eur.), residual solvents (GC).

The specification limits for the active substance are based on the monograph for docetaxel anhydrous in the European Pharmacopoeia and ICH Q6A recommendations.

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

The methods are described satisfactorily.

Results of analysis have been provided on three validation batches. All batches comply with the specifications.

Stability

Docetaxel in double packed in a food grade LDPE zipper bag, which is further packed in a LDPE bag and heat sealed. The material is then placed in a triple laminated Aluminium pouch and heat sealed. The pouch is finally packed in an opaque fibre-board drum. The specifications for the packaging materials have been provided and are in compliance with the Ph. Eur. monograph for polyolefines and the EU directive (2002/72/EC).

Stability studies were conducted on three validation batches and stored at accelerated (25°C ± 2°C, 60 ± 5 % RH) and long term (2°C-8°C) conditions.

Based on six months accelerated (25°C±2°C, 60 ± 5 % RH) and long term (2°C to 8°C) stability data, it is concluded that docetaxel is a stable drug substance when stored at proposed storage condition.

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

2.2.3. Finished medicinal product

Docetaxel Kabi is a clear, colourless to pale yellow solution, supplied in vials as a sterile, concentrate for solution for infusion containing 80 mg/4 ml, 120 mg/6 ml, 160 mg/8 ml or 180 mg/9 ml of drug substance Docetaxel. The proposed medicinal product is intended for dilution before infusion into an infusion bag containing 0.9% sodium chloride solution or 5% dextrose solution to give the final solution for infusion (between 0.3 mg/ml to 0.74 mg/ml of docetaxel).

The medicinal product comprises the following excipients: purified polysorbate 80, ethanol anhydrous and anhydrous citric acid.

Docetaxel concentrate for solution for infusion is filled in a 6 ml or 10 ml colourless Ph.Eur. Type-I glass vial, closed with a 20 mm flurotec rubber stopper and sealed with flip-off aluminium seal.

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 drug product is presented as a concentrate for solution for infusion, available in four dosages corresponding to 80 mg/4 ml, 120 mg/6 ml, 160 mg/8 ml and 180 mg/9 ml of anhydrous docetaxel.

The composition of the generic formulation is qualitatively identical to the reference product. The concentration of Polysorbate 80 in the finished product is the same as that of the reference product. Docetaxel is dissolved in a mixture of Polysorbate 80 and dehydrated alcohol in both the generic and reference products.

The aim of the formulation development was to develop the medicinal product as a stable sterile concentrate. It was therefore decided to solubilise the drug substance in an aqueous micellar system. Moreover, dilutions in 0.9% sodium chloride or in 5% glucose had also to be stable.

It was determined that the impurity profile of docetaxel concentrate for solution was adequate, and comparable to that of reference product Taxotere, when the product was prepared using purified polysorbate 80 with pH adjustment using citric acid. The Committee recommends conducting additional stability studies on one batch of drug product prepared with purified Polysorbate 80 having specified quality characteristics and comparing the generic product to the reference product. This request is included in the list of recommendations.

Aseptic processing including sterile filtration was selected for the manufacture of the sterile medicinal product. The active substance was dissolved in a mixture of dehydrated alcohol and purified polysorbate 80 followed by addition of anhydrous citric acid.

Given the poor solubility of docetaxel in the infusion fluids 0.9% sodium chloride and 5% dextrose, the formation of micelles in the final solution for infusion, their size and size distribution as well as their stability over time, are important factors for the bioavailability of docetaxel. Moreover, to fully establish the similarity after dilution between proposed product and reference product Taxotere, the micelle characteristics were assessed and compared. The mean size and size distribution of the dispersed micelles in the generic product were found to be similar to that in the reference product. It has also been confirmed that the active substance is fully solubilised upon dilution.

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 human or animal origin.

Manufacture of the product

Manufacturing process of Docetaxel 20 mg/ml concentrate for solution for infusion is classified as non-standard. The manufacturing process consists of four main steps: preparation of the bulk solution, sterile filtration (0.2 µm), aseptic filling, followed by closing the vials and packaging. The drug product is aseptically manufactured as it is not stable at high temperature to allow final sterilization.

The manufacturing process validation has been performed using three bulk finished product batches and was successfully completed. All parameters assessed during all stages of manufacturing from compounding to visual inspection of the sealed vials were within the specified criteria.

Product specification

The specifications for Docetaxel 20 mg/ml concentrate for solution for infusion include test for: appearance of solution (visual examination), identification of docetaxel (HPLC and UV), pH (Ph.Eur.), water content (Karl Fisher), ethanol content (GC), extractable volume (Ph.Eur.), colourimetry (UV visible), particulate contamination (Ph.Eur.), sterility (Ph.Eur.), bacterial Endotoxins (Ph.Eur.), seal integrity test (visual examination), related substances (HPLC), assay (HPLC).

The limits for the related substances are based on drug substance specification on the recommendations of ICH Q3B (R2) and are compliant with the requirement of CPMP/ICH/2738/99 'Note for guidance on impurities in new drug products'.

The specification for docetaxel content meets the requirements of Directive 2003/63/EC section 3.2.2.5 'Control of the finished medicinal products'. All other specifications comply with the Eur. Ph.

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

Batch results were provided for three bulk batches of the finished product. The results are in compliance with the proposed specification.

Stability of the product

Stability studies were performed under ICH long-term and accelerated conditions (25°C/60% RH, and 40°C/75% RH). Stability studies were performed on 12 prospective process validation batches (3 batches for each strength prepared from full scale solution batches).

Compatibility with infusion solvents and respective storage instructions were adequately addressed. The results indicate that the mean size and size distribution of the dispersed micelles in the generic product are similar to that in the reference product and indicate that the amount of drug solubilised in the diluted generic product is similar to that in the diluted reference product.

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. The 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 recommendation described in the SmPC, have been compared. Moreover, comparative plasma protein binding study of the generic and reference product was also performed in human plasma. No significant difference was observed from the comparative studies between the generic product and the reference product.

Therefore, similarity between Docetaxel Kabi and the reference product Taxotere can be accepted and no 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.

The CHMP has identified the following measures necessary to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product:

2.2.6. Recommendation 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:

The CHMP recommends that additional stability studies are performed on one batch of drug product prepared with purified Polysorbate 80 having specified quality characteristics and compared to the stability of the reference product.

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 Kabi manufactured by Fresenius Kabi Oncology Plc 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

Comparative experimental data regarding the physicochemical parameters and impurity profile before and after dilution in the two solvents recommended in the SmPC, in particular, mean size, size distribution and stability of the micelles that are formed in the final solution before intravenous administration have been compared. Moreover, comparative plasma protein binding study of the generic and reference product was also performed in human plasma. No significant difference was observed from the comparative studies between the generic product and the reference product (see Quality section).

Therefore, similarity between Docetaxel Kabi 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 Kabi was provided accepted by the CHMP. The summary of literature referred to the proposed indications:

<u>Breast cancer</u>

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

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

Gastric adenocarcinoma

Docetaxel Kabi 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 Kabi 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 current application concerns the product docetaxel, an active substance that has been in use for many years, and which 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, and therefore a Risk Minimisation Plan is not considered appropriate.

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 and focus test making reference to the Corporate layout of other product of similar drug class. The bridging report and focus test 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 treatment of breast cancer, non-small lung cancer, prostate cancer, gastric adenocarcinoma, head and neck cancer. No nonclinical 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.

Comparative experimental data regarding the physicochemical parameters and impurity profile before and after dilution in the two solvents recommended in the SmPC, in particular, mean size, size distribution and stability of the micelles that are formed in the final solution before intravenous administration have been compared. Moreover, comparative plasma protein binding study of the generic and reference product was also performed in human plasma. No significant difference was observed from the comparative studies between the generic product and the reference product (see Quality section).

Therefore, on the basis of the data submitted, not significant difference are shown between Docetaxel Kabi and the reference product Taxotere and therefore these can be accepted and no additional human bioequivalence study was considered necessary in this particular case.

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 Kabi in the 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.