25 June 2015
EMA/CHMP/289489/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Docetaxel Hospira UK Limited

International non-proprietary name: docetaxel

Procedure No. EMEA/H/C/003925/0000

Note

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

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List of abbreviations

ASMF	Active substance master file
CQA	Critical Quality Attribute
DSC	Differential scanning calorimetry
FT-IR	Fourier transform infrared spectroscopy
GC	Gas chromatography
HPLC	High Performance Liquid Chromatography
KF	Karl Fischer titration
MS	Mass Spectrometry
NMR	Nuclear magnetic resonance
Ph. Eur.	European Pharmacopoeia
QTPP	Quality Target Product Profile
RH	Relative Humidity
TGA	Thermal gravimetric analysis
TLC	Thin Layer Chromatography
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Hospira UK Limited submitted on 3 June 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Docetaxel Hospira UK Limited, 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 29 January 2014.

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 indications: breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma and 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.

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/ml concentrate for solution for infusion.
- Marketing authorisation holder: Aventis Pharma S.A
- Date of authorisation: (27-11-1995)
- Marketing authorisation granted by:
  - Community

Community Marketing authorisation number: EU/1/95/002/004

- 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/ml concentrate for solution for infusion.
- Marketing authorisation holder: Aventis Pharma S.A
- Date of authorisation: (27-11-1995)
- Marketing authorisation granted by:
  - Community

Community Marketing authorisation numbers: EU/1/95/002/002, EU/1/95/002/003, EU/1/95/002/004, EU/1/95/002/005

Information on paediatric requirements

Not applicable

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

Manufacturers responsible for batch release

HOSPIRA UK LIMITED
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
United Kingdom

Hospira Enterprises B.V.
Randstad 22-11
NL-1316 BN Almere
The Netherlands

1.3. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP:

Rapporteur: Milena Stain

- The application was received by the EMA on 3 June 2014.
- The procedure started on 25 June 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 September 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 October 2014.
- During the meeting on 23 October 2014, 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 23 October 2014.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 January 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 March 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 12 March 2015.
- During the CHMP meeting on 26 March 2015, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 17 April 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 April 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 7 May 2015.
- During the CHMP meeting on 21 May 2015, the CHMP agreed on 2nd List of outstanding issues to be addressd by the Applicant.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 5 June 2015.
- During the meeting on 25 June 2015, 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 Hospira UK Limited.

2. Scientific discussion

2.1. Introduction

Docetaxel Hospira UK Limited concentrate for solution for infusion is a generic medicinal product containing the active substance docetaxel. Docetaxel is a semi-synthetic taxoid derived from a non-cytotoxic precursor (10-deacetyl baccatin III), which is extracted from the needles of Taxus baccata and esterified with a chemically synthesised side chain.

The reference medicinal product is Taxotere, concentrate for solution for infusion, authorised on 27 November 1995. Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments.

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 Hospira UK Limited are identical to the indications of Taxotere and are as follows:

<u>Breast cancer</u>

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

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

Gastric adenocarcinoma

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

Docetaxel is administered as a one-hour infusion every three weeks. The recommended dose varies according to the indication (see SmPC section 4.2).

Docetaxel Hospira UK Limited 20 mg/1 ml concentrate for solution for infusion requires no prior dilution with a solvent and is ready to be added to the infusion solution. The required volume of Docetaxel Hospira UK Limited concentrate for solution for infusion must be injected via a single infusion (one shot) into a 250 ml infusion bag or bottle containing either 5% glucose solution or sodium chloride 9 mg/ml (0.9%) solution for infusion. If a dose greater than 190 mg of docetaxel is required, a larger volume of the infusion vehicle has to be used, so that a concentration of 0.74 mg/ml docetaxel is not exceeded (see SmPC section 6.6).

The single-dose vial Taxotere product is available in three presentations on the European market: 20 mg/1 ml, 80 mg/4 ml and 160 mg/8 ml. The proposed presentations of Docetaxel Hospira UK Limited are: 20 mg/1 ml, 80 mg/4 ml, and 120 mg/6 ml. Thus, Docetaxel Hospira UK Limited has an additional presentation of 120 mg/6 ml compared to Taxotere, which has been developed by Hospira based on considerations of market requirements. The proposed 120 mg/6 ml presentation has the same concentration of active ingredient per ml as the other presentations of Taxotere and is consistent with the dosage regimen and duration of use.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as 20 mg/mL concentrate for solution for infusion containing docetaxel (as trihydrate) as active substance. The other ingredients are polysorbate 80, ethanol (anhydrous) and citric acid monohydrate.

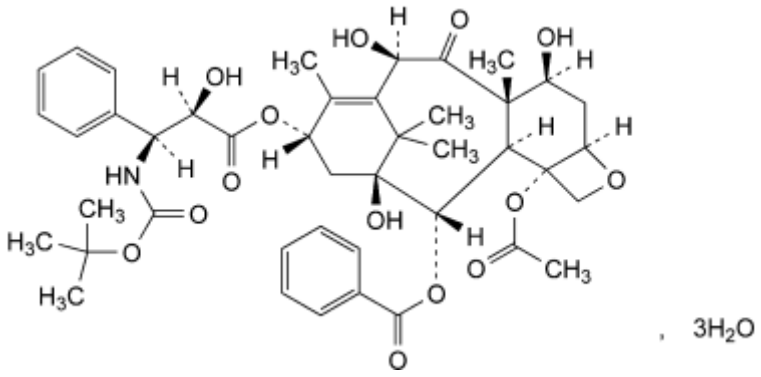
The product is available in clear glass (type I) vial with a chlorobutyl rubber stopper and an aluminium seal with a flip-off cap, containing 1 mL, 4 mL or 6 mL of concentrate.

Docetaxel Hospira UK Limited is diluted prior administration with either 0.9% sodium chloride or 5% glucose solutions.

2.2.2. Active substance

General information

The chemical name of docetaxel trihydrate is 5β,20-epoxy-1,7β,10β-trihydroxy-9-oxotax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-[(2*R*,3*S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-3-phenylpropanoate] trihydrate and it has the following structure:



The structure has been confirmed by elemental analysis, ultraviolet (UV) and infrared (IR) spectroscopy, mass spectrometry (MS), nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectroscopy and specific optical rotation. In addition, thermal (TGA and DSC) and XRD analysis were conducted to confirm its structural conformance to the Ph. Eur. reference standard.

Docetaxel trihydrate is a white or almost white, non-hygroscopic, crystalline powder, with a molecular mass of 861.93 $gmol^{-1}$, corresponding to the molecular formula $C_{43}H_{53}NO_{14}.3H_2O$. It is practically insoluble in water, freely soluble in anhydrous ethanol, soluble in dichloromethane.

Docetaxel trihydrate exhibits stereoisomerism due to the presence of eleven chiral centres. Enantiomeric purity is controlled routinely by specific optical rotation.

Polymorphism has been observed for docetaxel trihydrate. XRD studies confirmed that the polymorph obtained is identical to the Ph. Eur. docetaxel reference standard.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture, characterization and process controls

The active substance is a semi-synthetic taxoid derived from a non-cytotoxic precursor (10-deacetyl baccatin II), which is extracted from the needles of *Taxus baccata* and esterified with a chemically synthesized side chain. The extraction and isolation steps to obtain this starting material have been adequately described and suitable IPCs and specifications have been set.

The description of the manufacturing process has been adequately described and satisfactory specifications have been set for reagents, solvents and starting materials used in the process. Adequate in-process controls are applied during the synthesis.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Detailed information on the manufacturing of the active substance by the proposed manufacturer has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for appearance, identification (specific optical rotation and FT-IR), appearance of solution, assay (HPLC), related substances (HPLC), heavy metals (Ph. Eur.), water content (KF), sulphated ash (Ph. Eur.), residual solvents (GC), microbial limits and bacterial endotoxins (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Analysis data on three commercial scale batches of the active substance manufactured by the proposed manufacturer have been provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions at 25 ºC / 60% RH and for up to up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The parameters tested and analytical methods used are the same as for release and were stability indicating. All the parameters remained within the predefined specification at all time points and no trends were observed.

In addition, forced degradation studies of docetaxel trihydrate were performed on one batch. Samples were stored under the conditions of heat, humidity and light. The results from these studies indicate that the active substance degrades under exposure to high temperature or strong light. Although docetaxel trihydrate does not degrade under high humidity conditions, it can absorb some moisture. Therefore, docetaxel trihydrate drug substance must be stored in an airtight container.

Overall, the stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Docetaxel Hospira UK Limited concentrate for solution for infusion is presented as a clear pale yellow to brownish yellow solution available in three dosage strengths: 20 mg1 mL; 80 mg/4 mL; 120 mg/6mL.

The quality target product profile (QTPP) was defined as a stable injectable intravenous solution similar to Taxotere 20 mg/mL concentrate for solution for infusion that meets compendial and other relevant quality standards.

The critical quality attributes (CQAs) identified were description, identification, pH, assay, ethanol content, related substances, particulate matter, extractable volume, sterility, bacterial endotoxins and leachables.

The formulation and manufacturing development have been evaluated through the use of risk assessment to identify the critical product quality attributes and critical process parameters. Risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development and process design. The critical process parameters have been adequately identified.

The excipients were selected based on the composition of the reference medicinal product. The excipients used in the formulation are polysorbate 80, citric acid monohydrate and ethanol anhydrous. Citric acid monohydrate is used as an acidifying and stabilizing agent, polysorbate 80 as a surfactant, and anhydrous ethanol as a solvent. All the excipients employed are widely used in parenteral dosage forms and comply with their Ph. Eur. monographs.

The active substance is insoluble in water and solubilisation is achieved by adding polysorbate 80 to the formulation. The amount of polysorbate 80 added allows micelles to form, thus solubilising the docetaxel and preventing precipitation. 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 physicochemical characterisation of the micelle solution included the determination of the micelle size

distribution in infusion solutions of 0.9% sodium chloride and 5% glucose at high and low docetaxel concentrations (spanning all potential infusion solution concentrations used in the clinic), assay, critical micelle concentration and free and bound active substance. Testing was conducted at the in-use limit of 6 h. These studies showed that both products are similar in terms of micellar characteristics, irrespective of drug concentration or infusion solution, over the six hour storage period.

Comparative batch analysis data on three commercial scale batches of Docetaxel Hospira UK Limited of each strength and five batches of Taxotere (80 mg/mL) were also presented.

Considering these *in vitro* results and the similarity of the generic and reference product formulations it was considered that a biowaiver for this 'complex' injectable was justified.

The choice of the sterilization method was performed in accordance with the EMEA Decision Trees for the Selection of Sterilisation Methods (CPMP/QWP/054/98). Since Docetaxel Hospira UK Limited 20 mg/ml is a non-aqueous liquid terminal sterilization by moist heat is not feasible. The drug product is sterilized by double filtration. The filters are sterilized using a moist heat sterilization cycle and the filters are tested before and after the filling process to verify integrity. The primary packaging is a clear glass (type I) vial with a chlorobutyl rubber stopper and an aluminium seal with a flip-off cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and it is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: dispensing of the active substance and excipients, solution compounding, double sterile filtration (0.2 µm), aseptic filling and labelling and packaging. The process is considered to be a non-standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (HPLC, TLC), assay (HPLC), related substances (HPLC), particulate matter (Ph. Eur.), ethanol content (GC), extractable volume (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

Batch analysis results are provided for three commercial-scale batches of each presentation of the finished product confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three commercial scale batches of each presentation of the finished product stored under long term conditions (25 ºC / 60% RH) for up to 18 months, and under accelerated conditions (40 ºC / 75% RH) for up to 6 months, according to the ICH guidelines, were provided. Samples were also stored under intermediate conditions for up to 12 months at 30 ºC / 75% RH. The batches of finished product were manufactured at the proposed commercial site and were packed in the primary packaging proposed for

marketing. Samples were tested for description, assay, related substances, particulate matter, ethanol content, sterility and bacterial endotoxins. The analytical procedures used are stability indicating. All batches remained with the specifications and comparable results to the reference medicinal product were obtained.

In addition, forced degradation studies on one lab scale batch on exposure to acid, base, oxidant, heat and light were performed. Epi-docetaxel (4-epidocetaxel) was the major degradant from the acid, base and oxidative degradations. Base degradation also generated two additional major impurities. No severe degradation was observed under UV and heat conditions. This study was employed to demonstrate the stability indicating nature of the assay HPLC method used.

An infusion stability study was also conducted to compare the stability of Docetaxel Hospira UK Limited and the reference medicinal product when diluted in 0.9% sodium chloride and 5% glucose. The infusion solutions were prepared at the lowest concentration of 0.3 mg/mL and the highest concentration of 0.74 mg/mL. The study was conducted in non-PVC bags for both infusion solutions and in glass bottles for the 5% glucose solution. Testing was conducted for appearance, pH, assay, related substance and particulate matter. The results showed that the Docetaxel Hospira UK Limited drug product is comparable to Taxotere and is stable in either solution and at each concentration for up to 48 hours when refrigerated (5±3 °C) and for up to 6 hours at room temperature (25±2 °C).

Based on available stability data, a shelf-life of 18 months stored below 25°C in the original package is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The active substance and finished product have been adequately described.

The medicinal product consists of a micellar solution. Development of the generic product was based on the formulation, dosage form, concentration and use of the reference product. The composition of the generic formulation is qualitatively identical and quantitatively nearly identical to the innovator product Taxotere concentrate for solution for infusion. No bioequivalence study has been submitted by the applicant to demonstrate the pharmaceutical equivalence of his product to the reference medicinal product. Comparative experimental data regarding the physicochemical characteristics, e.g. micelle size distribution, critical micellar concentration, potency in the product ready to use (after dilution with 0.9% sodium chloride or 5% glucose) and impurity profile have been provided. No significant differences were observed from the comparative studies between the generic product and the reference product. Therefore, similarity between Docetaxel Hospira UK Limited and the reference product Taxotere can be accepted and no human bioequivalence study has been considered necessary.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The finished product is manufactured by aseptic filling which is 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.

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. Recommendation for future quality development

n/a

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.

According to ICH Q 3 B (R2), the applicant has provided a toxicological expert statement to support the qualification of impurities (see also quality aspects). 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 and accepted by the CHMP as the introduction of Docetaxel Hospira UK Limited manufactured by Hospira UK Limited 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 relevant SmPC sections are in line with the SmPC of the reference product.

No formal scientific advice by the CHMP has been requested for this medicinal product.

Exemption

No bioequivalence studies have been conducted. The Applicant outlined that docetaxel injection 20 mg/mL is a non-aqueous micelle forming formulation 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.

The applicant justified that the criteria of the above referred Guideline are met for Docetaxel Hospira UK Limited as detailed below:

- Rapid disassembly of the micelle on dilution occurs: Polysorbate 80 is rapidly cleared, after intravenous administration, by plasma carboxylesterases. This fact is adequately documented by scientific literature (Baker S Zhao M et al.). Docetaxel Hospira UK Limited is not designed to control release or disposition.
- Docetaxel Hospira UK Limited has the same active and inactive ingredients, indications, route of administration, dosage form and strength as Taxotere.
- The excipients do not affect the disposition of the drug substance.
- Physicochemical characteristics:

Studies regarding micelle size and micelle distribution in diluted solutions (dilution was done in 0.9% NaCl and in 5% glucose solution) were performed. The micelle size and distribution were tested within 6 hours of initial dosing of infusion bags using dynamic light scattering. The results of the dynamic light scattering study showed the similarity of both products (Taxotere, Docetaxel Hospira UK Limited) with regard to micelle size and size distribution at concentrations of 0,74 mg/mL and 0,3 mg/mL in 0,9% NaCl and in 5% Glucose solutions

An equilibrium dialysis method was developed and used to compare the extent of docetaxel protein binding to human plasma *in vitro* from Docetaxel Hospira UK Limited Injection or Taxotere. Results of this study clearly showed that the percent unbound docetaxel is similar between both drug products.

The Critical Micelle Concentration (CMC) for PS80 has been reported as 13 to 15 µg/mL or 23 to 37 mcg/mL in the literature (Product Information Tween 80 Sigma Ultra (P8074); Patist A, Bhagwat SS, Penfield KW et al.). At the recommended docetaxel concentration range in infusion solutions (approximately 0.3 mg/mL to 0.7 mg/mL), the concentration of PS80 is approximately 7,800 µg/mL to 19,240 µg/mL. Therefore, the concentration of PS80 in Docetaxel Hospira UK Limited Injection 20 mg/mL is significantly higher than the concentration at which PS80 forms micelles in aqueous solution. It should be noted that this concentration is highly similar to the PS80 concentration derived from dilution of Taxotere. Consequently, the quantity of PS80 in Docetaxel Hospira UK Limited formulation, which is highly similar to that found in Taxotere, on a mg PS80 per mg docetaxel basis is well in excess of that required to form micelles in docetaxel solutions. Therefore, no difference in micelle characteristics would be expected between Docetaxel Hospira UK Limited product and Taxotere.

Based on the Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (EMA/CHMP/QWP/799402/2011) which states that the same surfactant is a condition and that formulations may be qualitatively identical, with small quantitative changes only, the Applicant provided tables showing the concentrations of all ingredients, not only in their product as presented for the market, but also in the infusion solution(s) immediately prior to administration to the patient.

The composition of Docetaxel Hospira UK Limited and Taxotere is qualitatively identical, with small quantitative changes only. There was a slight difference in the content of Polysorbate 80 (Taxotere: 540 mg/ml vs Docetaxel Hospira UK Limited: 520 mg/ml), which is not likely to have a significant impact on micellar stability or disposition of the drug. A small quantitative difference is acceptable since the great dilution factor upon infusion to the patient would probably reduce any effects below the threshold of clinical relevance.

The infusion solutions from the Hospira product have higher amount in citric acid compared to those derived from Taxotere but as shown in the micelle characterization study this difference has no impact on micelle characteristics.

A comprehensive discussion on the safety implications of differences in composition was also provided by the Applicant. Citric acid is not considered to affect the safety or efficacy profile, especially when the drug is diluted and later injected into systemic circulation. The slight difference in the content of Polysorbate 80 is also not considered to affect the safety.

Taken all these data into consideration, the biowaiver requirements for micelle forming formulations as described in the "Guideline on the investigation of Bioequivalence (CPMP/QWP/EWP/1401/98/Rev1)" are considered met. Furthermore, the Applicant's development program is in line with recommendations made in the "Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems". Therefore, no additional human bioequivalence study was considered necessary in this particular case.

The additional "pack size" presentation of 120 mg/6 ml Docetaxel Hospira UK Limited has the concentration of active ingredient same (per ml basis) as the other presentations of the innovator product Taxotere, therefore, a waiver is accepted.

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 Hospira UK Limited was provided and was accepted by the CHMP. The summary of literature referred to the proposed indications:

Breast cancer

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

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

Gastric adenocarcinoma

Docetaxel Hospira UK Limited 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 Hospira UK Limited 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.

Overall, the Applicant provided an adequate clinical overview which supports the indications and covers the pharmacology, efficacy and safety of docetaxel. This is in accordance with the relevant guidelines 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.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• *Myelosuppression and complications* • *Severe hypersensitivity reactions* • *Severe cutaneous reactions such as eruptions/desquamations, Stevens Johnson syndrome (SJN) and Toxic Epidermal Necrolysis (TEN)* • *Severe fluid retention pleural effusion, pericardial effusion, ascites* • *Severe respiratory disorders* • *Severe cardiac disorder such as congestive heart failure or Myocardial infarction (MI)* • *Cystoid macular oedema (CMO)* • *Severe gastrointestinal events and complications; Colitis, GI perforation, GI haemorrhage* • *Severe peripheral neuropathy* • *Severe hepatic impairment* • *Delayed myelodysplasia or myeloid leukemia*
Important potential risks	• *Foetal harm* • *Male fertility*

Missing information	• *Use in patients with renal impairment* • *Lactation* • *Use in children aged 1 month to less than 18 years with nasopharyngeal carcinoma* • *Use in combination with other anti-cancer drugs for the treatment of breast cancer, non-small cell lung cancer, prostate cancer and head and neck cancer in patients with severe hepatic impairment*
Important identified interactions	• *Increased docetaxel toxicity when concomitant administration of strong CYP3P4 (antifungals, ritonavir, and macrolides)*

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Myelosuppression and complications	Proposed text in the SPC	None
Severe hypersensitivity reactions	Proposed text in the SPC	None
Severe cutaneous reactions such as eruptions/desquamations, Stevens Johnson syndrome (SJN) and Toxic Epidermal Necrolysis (TEN)	Proposed text in the SPC	None
Severe fluid retention pleural effusion, pericardial effusion, ascites	Proposed text in the SPC	None
Severe respiratory disorders	Proposed text in the SPC	None
Severe cardiac disorder such as congestive heart failure or Myocardial infarction (MI)	Proposed text in the SPC	None
Cystoid macular oedema (CMO)	Proposed text in the SPC	None
Severe gastrointestinal events and complications; Colitis, GI perforation, GI haemorrhage	Proposed text in the SPC	None
Severe peripheral neuropathy	Proposed text in the SPC	None
Severe hepatic impairment	Proposed text in the SPC	None
Delayed myelodysplasia or myeloid	Proposed text in the SPC	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
leukemia		
Foetal harm	Proposed text in the SPC	None
Male fertility	Proposed text in the SPC	None
Use in patients with renal impairment	Proposed text in the SPC	None
Lactation	Proposed text in the SPC	None
Use in children aged 1 month to less than 18 years with nasopharyngeal carcinoma	Proposed text in the SPC	None
Use in combination with other anti-cancer drugs for the treatment of breast cancer, non-small cell lung cancer, prostate cancer and head and neck cancer in patients with severe hepatic impairment	Proposed text in the SPC	None
Increased deocetaxel toxicity when concomitant administration of strong CYP3P4 (antifungals, ritonavir, and macrolides)	Proposed text in the SPC	None

2.7. PSUR submission

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

2.8. Product information

Given the presence in several Member States of a nationally approved Hospira product containing docetaxel with a similar name but different concentrations to the ones applied for Docetaxel Hospira UK Limited, measures have been taken by the Applicant to address the risk of potential medication errors. In particular, the Applicant has provided mock-ups for the packaging materials that sufficiently differentiate the product from the nationally authorised product with a different concentration.

Hospira UK Limited have informed the Agency that they will apply to change the name of the product from "Docetaxel Hospira UK Limited" to an NRG-approved invented name, together with a new labelling proposal. In addition, the concentration of the 20 mg/ml product will be displayed more prominently and in bold on the pack. Updated mock ups will be submitted by the applicant once the new invented name is available.

2.8.1. User consultation

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 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 Hospira UK Limited is administered as a non-aqueous micelle forming formulation, the Applicant provided comparative physicochemical data on micelle size and distribution after 6 hours as well as comparative data on the extent of docetaxel protein binding to human plasma *in vitro.* Based on these data, Docetaxel Hospira UK Limited pharmacokinetics, micelle 'disassembly' and docetaxel protein binding are considered comparable to Taxotere.

The formulation of Docetaxel Hospira UK Limited and Taxotere is qualitatively identical with small quantitative differences (in content of Polysorbate 80 and acid citric). However, these differences were not considered clinically relevant and thus considered acceptable.

Overall, there were no significant difference shown between Docetaxel Hospira UK Limited and the reference product Taxotere. Therefore, no additional human bioequivalence study was considered necessary.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

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 Hospira UK Limited 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

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.