7 June 2016
EMA/434463/2016
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Docetaxel SUN

International non-proprietary name: docetaxel

Procedure No. EMEA/H/C/004086/0000

Note

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

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List of abbreviations

AEs	Adverse events
AP	Applicant's part
AUC0-72h	Area under the concentration curve (AUC- calculated by the linear trapezoidal rule) from time zero to 72 hours
BE	Bioequivalence
CEP	Certification of Suitability (to the monographs of the European Pharmacopoeia)
CI	Confidence interval
Cmax	Maximum measured plasma concentration over the time span specified
CV	Coefficient of variation
CYP	Cytochrome P450 isoenzymes
EDQM	European Directorate for the Quality of Medicines
EPAR	European Assessment Report
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good Manufacturing Practice
IS	Internal standard
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
RP	Restricted part
RSD	Relative standard deviation
QC	Quality control
SmPC	Summary of product characteristics
Tmax	Time of the maximum measured plasma concentration

1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the generic application for Docetaxel SUN in the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, head and neck cancer is **not approvable** since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions.

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Major objection 1: Regarding the waiver of bioequivalence studies it is important to highlight that this product is not an aqueous intravenous solution, but a micellar solution. Therefore, the Applicant´s justification for the exemption of a bioequivalence study is not appropriate. The Applicant is requested to provide further physicochemical data to support an appropriate justification for not conducting a bioequivalence study and for the lack of clinical studies. In particular, comparative data should be submitted on:

- *mean size and size distribution of the dispersed micellar component*
- *estimated concentration of micellar entities, reflecting the extent (amount) of the micellar component.*
- *[free] vs [solubilised] fractions of the active substance.*

Questions to be posed to additional experts

None.

Inspection issues

GMP inspection(s)

N/A

GCP inspection(s)

N/A

2. Executive summary

2.1. Problem statement

N/A

2.2. About the product

Docetaxel, a semisynthetic taxoid, is a chemotherapy drug indicated for the treatment of breast cancer, non-small cell lung cancer (NSCLC), prostate cancer, gastric adenocarcinoma, and head and neck cancers as a single agent or in combination with other chemotherapeutic agents.

Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments. Docetaxel has been shown in vitro to disrupt the microtubular network in cells which is essential for vital mitotic and interphase cellular functions.

The product is to be administered as an aqueous intravenous (IV) solution containing the same active drug substance in the same concentration as the currently authorised product, Taxotere.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The applicant did not receive Scientific Advice from the CHMP.

2.4. General comments on compliance with GMP, GLP, GCP

No issues that would trigger a GMP inspection have been identified during the assessment of the information in Module 3 of the dossier.

No non-clinical or clinical studies are performed for this generic application; accordingly there are no GLP or GCP issues to be discussed.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

  This application for a marketing authorisation for Docetaxel SUN, 20 mg/ml, 80 mg/4 ml and 160 mg/8 ml, concentrate for solution for injection, is submitted under Article 10(1) (generic of a reference medicinal product) of Directive 2001/83/EC as amended.

  The reference/originator product is Taxotere concentrate for solution for infusion, authorised in the EU since 27th November 1995 through a centralised procedure (EU/1/95/002/003-5).

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

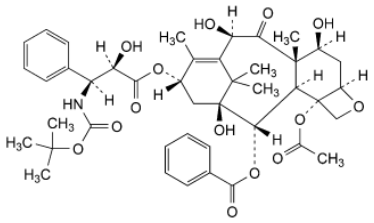
Docetaxel SUN 20 mg/1 ml, 80 mg/4 ml and 160 mg/8 ml, concentrate for solution for infusion is a clear yellowish solution presented in colourless glass vials closed with rubber stoppers and aluminium seals.

Prior to administration, the drug product concentrate is diluted by adding the prescribed amount of drug product concentrate directly into the infusion bag or bottle containing either 5% glucose or 0.9% sodium chloride solution for infusion.

3.1.2. Active Substance

General Information

Docetaxel anhydrous is described in Ph. Eur. The chemical name is 5β,20-Epoxy-1,7β,10β-trihydroxy-9-oxotax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-[(2R,3S)-3-[[(1,1-dimethylethoxy) carbonyl] amino]-2-hydroxy-3-phenylpropanoate] and the structure is shown below:



It is a white, crystalline, hygroscopic powder with low solubility in water but it is soluble in anhydrous ethanol and methylene chloride.
The CEP procedure is followed for documentation of the drug substance and a CEP is provided by the Applicant.

Manufacture, characterisation and process controls

The drug substance is manufactured two manufacturers by Hubei Haosun Pharmaceutical Co., Ltd., China (docetaxel anhydrous) and Shanghai Bioman Pharma Limited, China (drug substance intermediate). The documentation for manufacturing has been assessed by EDQM. However, the Applicant needs to provide updated GMP declaration from the drug product manufacturer.

Specification

According to the CEP, the Ph. Eur. monograph is to be supplemented by tests for residual solvents. The Applicant has also included test for microbial quality in the drug substance specification. For some of the tests the Applicant refers to USP methods and for these tests the Applicant is asked to demonstrate equivalence to Ph. Eur. tests. Additional batch analysis data are requested since compliant batch analysis data is provided for one drug substance batch only.

Stability

A retest period is not stated on the CEP but the Applicant has included stability data in the current MAA and a retest period is proposed. However, the Applicant needs to provide additional stability information before a retest period can be approved.

Comparability exercise for Active Substance

Not applicable.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Docetaxel SUN 20 mg/1 ml, 80 mg/4 ml and 160 mg/8 ml, concentrate for solution for infusion is a sterile clear yellowish solution. The container closure system consists of a colourless glass vial Type I closed with grey bromobutyl rubber stopper and sealed with aluminium caps with plastic flip off tops. Prior to administration, the drug product concentrate is diluted by adding the prescribed amount of drug product concentrate directly into the infusion bag or bottle containing either 5% glucose or 0.9% sodium chloride solution for infusion.

The developed product has the same dosage form, essentially the same composition and similar container closure system as the reference product. The anhydrous form of the active substance docetaxel is used in the generic product whereas the reference product contains docetaxel trihydrate.

The excipients used are polysorbate 80, ethanol anhydrous, citric acid anhydrous, and nitrogen, the same as for the reference product. Polysorbate 80 and ethanol are solubilisers, citric acid is stabilizer and nitrogen is used to protect against oxygen exposure. All excipients are widely used in parenteral dosage forms and comply with their respective Ph.Eur. monograph. The control of excipients should be amended with control of microbial quality, and more information should be provided on the quality of polysorbate 80 required for the use in this drug product.

Docetaxel is a low-aqueous solubility drug that is solubilized by micelle formation with polysorbate 80 upon dilution to allow intravenous administration. Comparable physicochemical properties with the reference product has been shown for description, assay of docetaxel, related substances, content of anhydrous ethanol and particulate matter. The applicant has however not provided any information or data documenting the micellar characteristics of this ‘complex’ product solution when ready for administration, compared to the reference product. Hence, characterisation of the complex aqueous micellar formulation and comparative in-vitro data to demonstrate equivalence of the proposed drug product with the reference product up to the end of administration are considered necessary in support of biowaver (see also overview on clinical aspects).

The manufacturing process development has in most parts been adequately described. Acceptable justification for sterilisation by sterile filtration followed by aseptic processing has been given. The active substance is prone to oxidation and nitrogen is therefore used during manufacture. The criticality of oxygen exposure should be discussed, and the control strategy should be further described.

The choice of container closure system and its suitability, and also the microbiological attributes are considered sufficiently documented.

Manufacture of the product and process controls

The manufacturing process comprises four main steps using non-standard process: preparation of the bulk solution, sterile filtration, aseptic filling of solution into sterile vials, stoppering and sealing.

The description of the manufacturing process and the control of critical steps are for most parts considered acceptable. Some further details should however be included in the process description with regard to conditions for bulk product preparation and filling, and also the sterility assuring steps and their control.

The presented results of process validation for three production scale batches of each presentation indicate that the manufacturing process is suitable to produce a consistant quality product complying with the defined in-process controls and the proposed finished product specifications.

Product specification

The control of the drug product is not acceptable yet, as a number of other concerns are raised.

The drug product specification cover appropriate parameters for this dosage form, except for clarity of solution and bacterial endotoxins that should be included. Also an additional specific identification test for docetaxel should be included. The specification limits for related substances should be tightened according to ICH guideline and batch data.

The analytical procedures are adequately described and validation in compliance with ICH guidelines is presented for relevant methods, except for that additional data and clarifications are required for the HPLC methods for assay and related impurities testing.

Results of batch analysis for three production scale batches of each strength show compliance with the proposed specifications. The results are well within the proposed specification, which provides support for the requested tightening of the drug product specification.

Some further information should be provided on characterisation of impurities, and also impurity profile compared to the reference product.

Stability of the product

The stability studies presented are performed in accordance with the respective ICH guideline at long term (25°C/60% RH), intermediate (30°C/65% RH) and accelerated (40°C/75% RH) conditions. The three validation batches of each presentation are placed on stability. Stability data for up to 9 months are currently available for the formal stability batches. Data up to 24 months real time storage have in addition been presented for development batches.

At long-term and intermediate storage conditions, all results on the formal stability batches are within the proposed shelf-life specification. Some degradation is seen for Impurity C of Ph.Eur. (4-epidocetaxel) and crotonaldehyde analog. No change seems to occur for the other specified impurities.

At the accelerated condition, OOS results for assay and unspecified related impurities are seen. Increase within the proposed shelf-life specification is seen for Impurity C and crotonaldehyde analog. The other specified impurities stay at or below 0.2%, and no increase seems to occur.

Results of forced degradation studies are presented as part of the HPLC method validation and it is concluded that the methods used for assay and impurity testing are stability indicating.

The results of the formal stability studies (up to 9 months storage) seen together with the stability data on development batches (up to 24 months storage), seems to indicate that a shelf-life longer than the proposed 12 months is achievable. Results of further stability time points available for the formal stability batches evaluated towards the updated drug product shelf-life specification should however be submitted before conclusion is drawn on shelf-life and temperature storage condition. The proposed temperature storage restriction “Do not store above 30 °C” seems to be supported. Results of photostability testing according ICH Q1B guidelines show that the drug product packed in the market pack is photostabile. The storage claim “Store in the original package in order to protect from light” is supported.

Comparability exercise for Finished Medicinal Drug Product

Not applicable.

Adventitious agents

Not applicable. None of the excipients used in the formulation of the drug product are of animal or human origin.

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

For both the active substance and the drug product a number of issues have been identified as summarised above and outlined in the list of questions.

Drug substance

The drug substance is described in Ph. Eur. One drug substance source is proposed and the CEP procedure is followed for documentation. Concerning the manufacturing site for the drug substance intermediate used by the drug substance manufacturer, the Applicant needs to provide updated GMP declaration signed by the QP of the drug product manufacturer.

The drug substance specification proposed by the Applicant includes all tests required by the CEP and in addition test for microbial quality. However, in the cases where the Applicant refers to USP methods the Applicant is asked to demonstrate equivalence to corresponding Ph. Eur. test methods.

Concerning the retest period proposed by the Applicant, there are several issues that need to be resolved before a retest period can be approved.

Drug product

The developed drug product has the same dosage form, essentially the same composition and similar container closure system as the reference product, Taxotere.

Comparable physicochemical properties with the reference product has been shown for description, assay of docetaxel, related substances, content of anhydrous ethanol and particulate matter. The applicant has however not provided any information or data documenting the micellar characteristics of this ‘complex’ product solution when ready for administration, compared with the reference product.

The description of drug product manufacture is for most parts adequate, but more details should be provided for conditions applied during bulk product manufacture and for process controls relating to assuring sterility.

The control of excipients should be amended with control of microbial quality, and more information should be provided on the quality of polysorbate 80 required for use in this drug product.

The control of drug product is not acceptable yet. The proposed specifications should be amended with tests for clarity of solution and bacterial endotoxins, and an additional specific identification test for docetaxel. The proposed specification limits for related substance both at release and during shelf life should be tightened to qualified levels and according to the data presented. A few clarifications are required for method description and validation for the HPLC method used for assay of docetaxel and for determination of related substances. Some further information should be provided on impurities compared to the reference product.

The container closure system is considered adequately described.

The results for up to 9 months storage from the formal stability studies indicate that a shelf-life of minimum 12 months is acceptable, with storage claims “Do not store above 30 °C” and “Store in the original package in order to protect from light”. Further data from the formal stability studies evaluated towards the amended shelf-life specification should however be provided to confirm shelf-life and temperature storage claim.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of the data on quality, it is considered that the application for Docetaxel SUN could be approvable. No MOs have been raised. Issues have however been identified both for drug substance and drug product that need to be resolved before approval can be recommended. It is expected that these issues can be resolved.

3.2. Non clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

The composition of Docetaxel SUN is essentially similar to the reference product (Taxotere) for both active and inactive ingredients. Therefore, there are no excipient concerns requiring safety assessment.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

Regarding the impurity profile it has to be mentioned that some limits for impurities are much wider than justified by the data presented by the applicant. These limits above the qualification threshold have to be toxicologically justified or otherwise qualified as described in the Quality Assessment Report (see LoQ).

The CHMP considers that the non-clinical overview is based on up-to-date and adequate scientific literature. It is agreed that no further non-clinical studies are required, provided that satisfactory data are submitted to justify the limits above the qualification threshold for the respective impurities.

3.2.1. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Docetaxel SUN 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.

3.2.2. Conclusion on non-clinical aspects

In principle there are no objections to approval of Docetaxel SUN from a non-clinical point of view and no MOs have been raised. However, the limits above the qualification threshold for some impurities have to be justified, as described in the Quality Assessment Report (see LoQ).

3.3. Clinical aspects

Exemption

Biowaiver

No bioequivalence studies have been conducted.

Docetaxel SUN has the same active and inactive ingredients, indications, route of administration, dosage form and strength as Taxotere, EU/1/95/002/003-5.

Compositions of the reference product, Taxotere, and of Docetaxel SUN, is presented in the tables below.

Sr. No.	Name of the ingredients	TAXOTERE® concentrate for solution for infusion (Each vial contains)		
		20mg/ml	80mg/4ml	160mg/8ml
1	Docetaxel	20 mg	80 mg	160 mg
2	Polysorbate 80*	540 mg	2160 mg	4320 mg
3.	Ethanol anhydrous	395 mg	1.58 g	3.16 g
	Citric Acid	----	----	----

* Consider specific gravity 1.08 of polysorbate 80 & Doc. Ref.: EMA/774786/2009

Sr. No.	Name of the ingredients	Docetaxel SUN concentrate for solution for infusion (Each vial contains)		
		20mg/ml	80mg/4ml	160mg/8ml
1	Docetaxel	20 mg	80 mg	160 mg
2	Polysorbate 80	540 mg	2160 mg	4320 mg
3.	Ethanol anhydrous	395 mg	1.58 g	3.16 g
	Citric Acid	4 mg	16 mg	32 mg

The applicant claims that no bioequivalence study is required for this application as the product is to be administered as an aqueous intravenous (IV) solution containing the same active drug substance in the same concentration as the currently authorised product, Taxotere.

3.3.1. Discussion on clinical aspects

Biowaiver

According to Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. The applicant's product Docetaxel SUN, concentrate for solution for injection, has the same active substance and the same excipients. The amount of citric acid in the reference product is not stated, but any difference in the amount of this excipient is not expected to have any clinical significance. Furthermore, the applied product has the same indications, posology, pharmaceutical form, route of administration and strength as Taxotere.

Docetaxel is a lipophilic molecule with a low-aqueous solubility. To allow administration of the drug by infusion, docetaxel is solubilized by micelle formation with polysorbate 80. As stated in the bioequivalence guideline, micelle solutions for intravenous administration may be regarded as 'complex' solutions and therefore normally do not qualify for a biowaiver.

To consider micelle formulations eligible for a biowaiver, several criteria have to be fulfilled.

In this case, the applied product fulfils the exception-criteria listed in the bioequivalence guideline; rapid disassembly of the micelle on dilution occurs and the drug product is not designed to control release or disposition, the method and rate of administration is the same as the currently approved product, and the excipients do not affect the disposition of the drug substance.

The applicant has not commented on the fact that this is a micellar solution, nor have they provided any data to demonstrate similar physiochemical characteristics between the products.

In accordance with the "Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems EMA/CHMP/QWP/799402/2011", a complete biopharmaceutical argument should be proposed together with the results of relevant physicochemical tests as bioequivalence surrogate markers. The level of testing depends on how similar the generic is to the reference product in terms of qualitative and quantitative composition. In this case, the composition is similar, with the same excipients in the same amounts with the possible exception of citric acid.

Before a conclusion on the acceptability of a biowaiver can be reached, results of comparative studies testing important characteristics of the micelle component in solutions immediately prior to injection/infusion according to the dilution/administration instructions in the SmPC should be presented.

In particular, comparative data must be submitted on:

- mean size and size distribution of the dispersed micellar component

- estimated concentration of micellar entities, reflecting the extent (amount) of the micellar component.

- [free] vs [solubilised] fractions of the active substance

Please also refer to the quality assessment.

3.3.2. Conclusions on clinical aspects

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. The proposed SmPC of the applied product is also in line with the SmPC of Taxotere.

Regarding the waiver of bioequivalence studies it is important to highlight that this product is *not* an aqueous intravenous solution, but a micellar solution. Hence, the applicant´s justification for the exemption of a bioequivalence study is not appropriate. The applicant is requested to provide further physicochemical data to support an appropriate justification for not conducting a bioequivalence study. This issue is currently raised as a Major Objection (please refer to proposed LoQ).

3.4. Risk management plan

Summary of safety concerns

The Applicant identifies the following safety concerns

Table 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Peripheral neuropathy (sensory/motor) • Respiratory disorders including radiation pneumonitis • Alcohol intoxication • Haemotological toxicity • Fluid retention • Hypersensitivity • Skin toxicity • Serious and fatal drug interactions involving CYP3A4 inhibitors
Important potential risks	• Cardiovascular toxicity including venous thromboembolic events • Thrombotic microangiopathy • Haemolytic uremic syndrome • Thrombotic thrombocytopenic purpura • Microangiopathic haemolytic anaemia • Cystoid macular oedema • Acute Leukemia/Myelodysplasia
Missing information	• Use in paediatric population • Use in renal impairment • Use in pregnancy/breast-feeding

Having considered the data in the safety specification, the CHMP considers that the following issues should be addressed:

- The Applicant should harmonise the safety specifications in line with the RMP of other docetaxel generics:

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)

- Additional risks to be proposed for inclusion into the safety specifications as identified or potential risks should be justified in accordance with the criteria set out in the GVP Module V Risk Management Systems.
- If a justification for inclusion as an important potential risk could be provided, the MAH should consider grouping haemolytic uremic syndrome, thrombotic thrombocytopenic purpura and microangiopathic haemolytic anaemia under the term "Thrombotic microangiopathy" in the RMP.

Pharmacovigilance plan

The PRAC, having considered the data submitted, is of the opinion that in line with the reference product Taxotere routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that in line with the reference product routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

However, the PhV plan should be updated along with the update of safety specification as recommended by the CHMP.

Risk Minimisation Measures:

Table 2: Proposal from applicant for risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Peripheral neuropathy (sensory/motor)	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in *Section 4.4 - Special warnings and precautions for use:* The development of severe peripheral neurotoxicity requires a reduction of dose. *Section 4.8 - Undesirable effects* Listed as frequently occurring adverse drug reactions. The development of severe peripheral neurotoxicity requires a reduction of dose. Mild to moderate neurosensory signs are characterised by paresthesia, dysesthesia or pain including burning. Neuro-motor events are mainly characterised by weakness.	Currently the available data does not support the need for additional risk minimization activities.
Respiratory disorders including radiation pneumonitis	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in *Section 4.4 - Special warnings and precautions for use:* Acute respiratory distress syndrome, interstitial pneumonia/pneumonitis,	Currently the available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	interstitial lung disease, pulmonary fibrosis and respiratory failure have been reported and may be associated with fatal outcome. Cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy. If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. Interruption of docetaxel therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming docetaxel treatment must be carefully evaluated. *Section 4.8 - Undesirable effects* Acute respiratory distress syndrome and cases of interstitial pneumonia/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure sometimes fatal have rarely been reported. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.	
Alcohol intoxication	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in *Section 4.4 - Special warnings and precautions for use:* This medicinal product contains	Currently the available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	50 vol% ethanol (alcohol), i.e. up to 0.395 g (0.5 ml) per vial, equivalent to 10 ml of beer or 4 ml wine per vial. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicinal products. The amount of alcohol in this medicinal product may impair the patient's ability to drive or use machines.	
Haematological toxicity	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in *Section 4.3 – Contraindications* Docetaxel should not be recommended to patients with baseline neutrophil count of < 1,500 cells/mm3. *Section 4.4 - Special warnings and precautions for use:* 1) Frequent monitoring of complete blood counts should be conducted on all patients receiving docetaxel. Patients should be retreated with docetaxel when neutrophils recover to a level ≥ 1,500 cells/mm3. 2) In the case of severe neutropenia (< 500 cells/mm3 for seven days or more) during a course of docetaxel therapy,	Currently the available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	a reduction in dose for subsequent courses of therapy or the use of appropriate symptomatic measures are recommended 3) Primary G-CSF prophylaxis should be considered in patients who receive treatment with TCF (docetaxel in combination with cisplatin and 5-fluorouracil) and TAC (docetaxel in combination with doxorubicin and cyclophosphamide) for breast cancer to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection) neutropenia or neutropenic infection). 4) Patients receiving TCF & TAC should be closely monitored *Section 4.8 - Undesirable effects* Anaemia and neutropenia were most commonly reported whereas thrombocytopenia was commonly reported adverse reactions of docetaxel alone or in combination which was reversible and the median duration of severe neutropenia (< 500 cells/mm3) was 7 days.	
Fluid retention	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in *Section 4.4 - Special warnings and precautions for use:* 1) Premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day or 3 days starting 1 day prior	Currently the available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	to docetaxel administration, unless contraindicated, must be considered to reduce the incidence and severity of fluid retention 2) Patients with severe fluid retention such as pleural effusion, pericardial effusion and ascites should be monitored closely. *Section 4.8 - Undesirable effects* Listed as very commonly occurring adverse drug reactions. It includes events such as peripheral oedema and less frequently pleural effusion, pericardial effusion, ascites and weight gain.	
Hypersensitivity	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in *Section 4.3 – Contraindications* Docetaxel should not be recommended in patients with hypersensitivity to the active substance or to any of the excipients *Section 4.4 - Special warnings and precautions for use:* 1) Premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, must be considered to reduce the incidence and severity of hypersensitivity reactions. 2) Patients should be observed closely for hypersensitivity reactions especially during the	Currently the available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	first and second infusions. 3) Interruption of docetaxel therapy is recommended for severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema. 4) Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel. *Section 4.8 - Undesirable effects* Listed as commonly occurring adverse drug reaction with docetaxel alone or in combination with other agents.	
Skin toxicity	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in *Section 4.4 - Special warnings and precautions for use* For patients who experience severe or cumulative cutaneous reactions, dose reduction or drug interruption/discontinuation should be considered.	Currently the available data does not support the need for additional risk minimization activities.
Serious and fatal drug interactions involving CYP3A4 inhibitors	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in *Section 4.4 - Special warnings and precautions for use:* The concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone,	Currently the available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided. *Section 4.5 - Interaction with other medicinal products and other forms of interaction* *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as ciclosporine, ketoconazole and erythromycin. As a result, caution should be exercised when treating patients with these medicinal products as concomitant therapy since there is a potential for a significant interaction. In case of combination with CYP3A4 inhibitors, the occurrence of docetaxel adverse reactions may increase, as a result of reduced metabolism. If the concomitant use of a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) cannot be avoided, a close clinical surveillance is warranted and a dose-adjustment of docetaxel may be suitable during the treatment with the strong CYP3A4 inhibitor. It was identified that theco-administration of docetaxel with the strong CYP3A4 inhibitor ketoconazole leads to a significant decrease in	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	docetaxel clearance by 49%.	
Cardiovascular toxicity including Venous thromboembolic events	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in *Section 4.4 - Special warnings and precautions for use:* Congestive heart failure has been observed in patients receiving docetaxel in combination with trastuzumab, particularly following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This may be moderate to severe and has been associated with death. Patients should undergo baseline cardiac assessment before initiating treatment with docetaxel in combination with trastuzumab Cardiac function should be further monitored during treatment (e.g. every three months) to help identify patients who may develop cardiac dysfunction	Currently the available data does not support the need for additional risk minimization activities.
Thrombotic microangiopathy	Close monitoring of the adverse event with cumulative periodic review.	Currently the available data does not support the need for additional risk minimization activities.
Haemolytic uremic syndrome	Close monitoring of the adverse event with cumulative periodic review.	Currently the available data does not support the need for additional risk minimization activities.
Thrombotic thrombocytopenic purpura	Close monitoring of the adverse event with cumulative periodic review.	Currently the available data does not support the need for additional risk minimization activities.
Microangiopathic heaemolytic anaemia	Close monitoring of the adverse event with cumulative	Currently the available data does not support the need for additional risk minimization

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	periodic review.	activities.
Cystoid macular oedema	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in *Section 4.4 - Special warnings and precautions for use:* Cystoid macular oedema (CMO) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated. *Section 4.8 - Undesirable effects* Cases of cystoid macular oedema (CMO) have been reported in patients treated with docetaxel.	Currently the available data does not support the need for additional risk minimization activities.
Acute Leukaemia/ Myelodysplasia	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in *Section 4.4 - Special warnings and precautions for use:* Risk of delayed myelodysplasia or myeloid leukaemia has been identified in patients treated with docetaxel, doxorubicin and cyclophosphamide (TAC) which further requires haematological follow-up. *Section 4.8 - Undesirable effects* *Post Marketing Experience* Cases of acute myeloid	Currently the available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	leukaemia and myelodysplastic syndrome have been reported in association with docetaxel when used in combination with other chemotherapy agents and/or radiotherapy.	
Use in paediatric population	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in *Section 4.2 - Posology and method of administration:* The safety and efficacy of Docetaxel in nasopharyngeal carcinoma in children aged 1 month to less than 18 years have not yet been established. There is no relevant use of Docetaxel in the paediatric population in the indications breast cancer, non-small cell lung cancer, prostate cancer, gastric carcinoma and head and neck cancer, not including type II and III less differentiated nasopharyngeal carcinoma.	Currently the available data does not support the need for additional risk minimization activities.
Use in renal impairment	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in *Section 4.4 - Special warnings and precautions for use:* There are no data available in patients with severely impaired renal function treated with docetaxel.	Currently the available data does not support the need for additional risk minimization activities.
Use in pregnancy/breastfeeding	Summary of Product Characteristics (SPC) of docetaxel has already been updated with the information on this safety concern in	Currently the available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.6 - Fertility, pregnancy *and lactation:* There is no information on the use of docetaxel in pregnant women. Docetaxel has been shown to be both embryotoxic and foetotoxic in rabbits and rats, and to reduce fertility in rats. As with other cytotoxic medicinal products, docetaxel may cause foetal harm when administered to pregnant women. Therefore, docetaxel must not be used during pregnancy unless clearly indicated. Women of childbearing age receiving docetaxel should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur. Docetaxel is a lipophilic substance but it is not known whether it is excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breast feeding must be discontinued for the duration of docetaxel therapy.	

The PRAC considered that the proposal are nearly acceptable but it is recommended that for ***each safety concern a table is detailing the risk minimisation measures*** which will be undertaken even if it is only routine risk minimisation activities.

The PRAC, having considered the data submitted, was of the opinion that the Summary table of Risk Minimisation Measures is acceptable.

The MAH should include this table as indicated in the template of the Guidance on format of the risk management plan (RMP) in the EU for generics – please note that routine pharmacovigilance is considered sufficient to measure the effectiveness.

A second table of Part V.1 of the RMP about the effectiveness of risk minimisation measures for each safety concern is missing.

Conclusion

The RMP could be acceptable provided an updated RMP and satisfactory responses to the list of questions below is submitted.

3.5. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

4. Benefit /risk assessment

The application contains adequate non-clinical data. Several Other Concerns are raised to the quality part that need to be resolved before approval can be recommended.

At present, a benefit/risk ratio comparable to the reference product cannot be concluded until further physicochemical data to support an appropriate justification for *not* conducting a bioequivalence study are provided; this issue is raised as a Major Objection.

4.1. Conclusions

The overall B/R of Docetaxel SUN is negative.

5. Recommended conditions for marketing authorisation and product information in case of a positive benefit risk assessment

*5.1. Proposed list of post-authorisation measures**

Post-authorisation measure(s)	Motivation
Proposed post-authorisation measure 1 with proposed classification:	Motivation/Background information on measure, including due date:
1.	
Proposed post-authorisation measure 2 with proposed classification:	Motivation/Background information on measure, including due date:
2.	
Proposed post-authorisation measure 3 with proposed classification:	Motivation/Background information on measure, including due date:
3.	
Proposed post-authorisation measure X with proposed classification:	Motivation/Background information on measure, including due date:
X.	

* Classification: category 1= Annex II D condition; category 2= Annex II E specific obligations; category 3 = All other studies reflected only in the RMP (non-clinical, PK, PASS)

Proposed list of recommendations:

Description of post-authorisation measure(s)
1.
2.

5.2. Other conditions

N/A

5.3. Summary of product characteristics (SmPC)

Please be informed that the European Medicines Agency and the Quality Review of Documents (QRD) Group have revised the Human Product Information templates.

The revised QRD template has introduced new guidance for 1) the acceptance of combined SmPCs for different strengths of the same pharmaceutical form, 2) the dates to be recorded in section 9 of the SmPC (i.e. date of first authorisation and date of latest renewal), 3) the text to be included in Annex II, and 4) the list of local representatives in the package leaflet as a result of the revised EC Guideline on the packaging information of medicinal products for human use.

Applicants should comply with the revised QRD template as early as possible and at the latest by Day 181 of the procedure (e.g. at Day 121 or at Day 181).

For further comments, please refer to the amended SmPC.

5.4. Labelling

5.5. Package leaflet (PL)

User consultation

The results of the readability test will be provided before day 121, as the Applicant expects the wording of the PIL to change during the procedure.