Public Assessment Report

Decentralised Procedure

TAXCEUS 20MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION (docetaxel)

Procedure No: UK/H/1793/001/DC

UK Licence No: PL 11587/0074

MEDAC GESELLSCHAFT FÜR KLINISCHE SPEZIALPRÄPARATE MBH
LAY SUMMARY
Taxceus 20mg/ml concentrate for solution for infusion
(docetaxel)

This is a summary of the public assessment report (PAR) for Taxceus 20mg/ml concentrate for solution for infusion. This summary explains how Taxceus 20mg/ml concentrate for solution for infusion was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Taxceus 20mg/ml concentrate for solution for infusion.

For practical information about Taxceus 20mg/ml concentrate for solution for infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is Taxceus 20mg/ml concentrate for solution for infusion and what is it used for?

Taxceus 20mg/ml concentrate for solution for infusion is a hybrid application. This means that Taxceus 20mg/ml concentrate for solution for infusion is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Taxotere 20mg concentrate and solvent for solution for infusion.

Taxceus 20mg/ml concentrate for solution for infusion is used alone or in combination with other anti-cancer medicines in the treatment of:
- breast cancer
- special forms of lung cancer (non-small cell lung cancer)
- prostate cancer (used in combination only)
- gastric cancer (used in combination only)
- head and neck cancer (used in combination only).

How is Taxceus 20mg/ml concentrate for solution for infusion used?

This is a prescription only medicine. Taxceus 20mg/ml concentrate for solution for infusion will be administered to you by a healthcare professional. The healthcare professional will calculate the body surface area in square meters in order to determine the correct dose. Taxceus 20mg/ml concentrate for solution for infusion is administered at a hospital by infusion into a vein. The infusion lasts approximately one hour.

How does Taxceus 20mg/ml concentrate for solution for infusion work?

Taxceus 20mg/ml concentrate for solution for infusion contains the active ingredient docetaxel. Docetaxel belongs to a group of anti-cancer medicines called taxoids. This medicine works by killing specific cancer cells.

How has Taxceus 20mg/ml concentrate for solution for infusion been studied?

Taxceus 20mg/ml concentrate for solution for infusion is a hybrid application; studies have been limited to tests to determine that it is comparable to the reference medicine, Taxotere 20mg concentrate and solvent for solution for infusion.

What are the benefits and risks of Taxceus 20mg/ml concentrate for solution for infusion?

Taxceus 20mg/ml concentrate for solution for infusion is a hybrid application and is comparable to the reference medicine. Therefore, the benefits and risks are taken as being the same as the reference medicine.
Why is Taxceus 20mg/ml concentrate for solution for infusion approved?

It was concluded that, in accordance with EU requirements, Taxceus 20mg/ml concentrate for solution for infusion has been shown to have comparable quality and to be comparable to Taxotere 20mg concentrate and solvent for solution for infusion. Therefore, the view was that, as for Taxotere 20mg concentrate and solvent for solution for infusion, the benefit outweighs the identified risks.

What measures are being taken to ensure the safe and effective use of Taxceus 20mg/ml concentrate for solution for infusion?

A risk management plan has been developed to ensure that Taxceus 20mg/ml concentrate for solution for infusion is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Taxceus 20mg/ml concentrate for solution for infusion, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Taxceus 20mg/ml concentrate for solution for infusion

Germany, Italy, the Netherlands and UK agreed to grant a Marketing Authorisation for Taxceus 20mg/ml concentrate for solution for infusion on 14 July 2010. A Marketing Authorisation was granted in the UK on 02 August 2010. A Marketing Authorisation was granted in the UK to Caduceus Pharma Limited on 2nd August 2010 (PL 24668/0149; UK/H/1793/001/DC). A change of ownership procedure was performed to Medac Gesellschaft für klinische Spezialpräparate mbH on 11 May 2011 (PL 11587/0074).

The full PAR for Taxceus 20mg/ml concentrate for solution for infusion follows this summary. For more information about treatment with Taxceus 20mg/ml concentrate for solution for infusion, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in 02-2014.
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III Scientific overview and discussion
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   III.2 Non-clinical aspects
   III.3 Clinical aspects
IV Overall conclusion and benefit-risk assessment

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## Module 1

### Information about initial procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Taxceus 20mg/ml concentrate for solution for infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic hybrid, Article 10.3</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Form</td>
<td>Concentrate for solution for infusion</td>
</tr>
<tr>
<td>Strength</td>
<td>20mg/ml</td>
</tr>
</tbody>
</table>
| MA Holder | Caduceus Pharma Ltd.
6th Floor, 94 Wigmore Street
London
W1U 3RF
United Kingdom |
| Reference Member State (RMS) | UK |
| CMS | UK/H/1793/01/DC: Germany, Italy, the Netherlands. |
| Procedure Number | UK/H/1793/001/DC |
| End of Procedure | Day 160 – 14th July 2010 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflet for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING
Carton

1. NAME OF THE MEDICINAL PRODUCT
Taxceus 20 mg/ml concentrate for solution for infusion
docetaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each ml of concentrate contains 20 mg of docetaxel.
One vial of 1 ml of concentrate contains 20 mg docetaxel.
One vial of 4 ml of concentrate contains 80 mg docetaxel.
One vial of 7 ml of concentrate contains 140 mg docetaxel.

3. LIST OF EXCipients
Contains citric acid anhydrous, povidone, polysorbate 80, ethanol absolute.

4. PHARMACEUTICAL FORM AND CONTENTS
1 x 20 mg/1 ml single dose vial
1 x 80 mg/4 ml single dose vial
1 x 140 mg/7 ml single dose vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read the package leaflet before use.
Must be diluted before use.
For intravenous use as infusion, after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
Cytotoxic agent

8. EXPIRY DATE
EXP
The diluted medicinal product should be used immediately.

9. **SPECIAL STORAGE CONDITIONS**

Store below 25°C
Store in the original package in order to protect from light.
Refer to the package leaflet for storage conditions after dilution.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Discard unused contents appropriately

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Caduceus Pharma Ltd
6th Floor, 94 Wigmore Street
London W1U 3RF
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 24668/0149

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Justification for not including Braille accepted
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Taxceus 20 mg/ml concentrate for solution for infusion
docetaxel
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
For infusion after dilution.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mg/1 ml single dose vial
80 mg/4 ml single dose vial
140 mg/7 ml single dose vial

6. OTHER

Cytotoxic agent
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Germany, Italy, the Netherlands and the UK considered that the application for Taxceus 20mg/ml concentrate for solution for infusion (PL 24668/0149; UK/H/1793/001/DC) could be approved. The product is a prescription-only medicine (POM) containing the active substance docetaxel and is indicated for the following:

- **Breast cancer**
  Adjuvant treatment of operable node-positive breast cancer (in combination with doxorubicin and cyclophosphamide).
  Locally advanced or metastatic breast cancer (in combination with doxorubicin for the treatment of patients with who have not previously received cytotoxic therapy for this condition).
  Locally advanced or metastatic breast cancer (as monotherapy or in combination with capecitabine after failure of cytotoxic chemotherapy).
  Locally advanced or metastatic breast cancer
  Metastatic breast cancer (in combination with trastuzumab for patients whose tumors over express HER2 and who have not received chemotherapy for metastatic disease).

- **Non-small cell lung cancer**
  Locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.
  Unresectable, locally advanced or metastatic non-small cell lung cancer (in combination with cisplatin in patients who have not previously received chemotherapy).

- **Prostate cancer**
  Hormone refractory metastatic prostate cancer (in combination with prednisone or prednisolone).

- **Gastric Adenocarcinoma**
  Metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction (in combination with cisplatin and 5-fluorouracil in patients who have not received prior chemotherapy for metastatic disease).

- **Head and neck cancer**
  Locally advanced squamous cell carcinoma of the head and neck (in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment).

This application for Taxceus 20mg/ml concentrate for solution for infusion is submitted as an abridged application according to Article 10.3 of Directive 2001/83/EC, a hybrid application for a product claiming essential similarity to Taxotere 20mg concentrate and solvent for infusion, first authorised in the EEA to Aventis Pharma S.A. in November 1995.

Docetaxel is a semi-synthetic taxane manufactured from a taxane precursor derived from the needles of the European yew tree *Taxus baccata*.
Docetaxel acts by promoting the assembly of microtubules and prevent their depolymerisation, thus interfering with a number of normal cellular functions. The microtubule assembly is stable and dysfunctional, leading to disruption of the normal microtubule dynamics that is required for cell division and vital processes during interphase.

In addition to the detailed review of the non-clinical properties of docetaxel in the open literature, the applicant has submitted comparative studies designed to detect similarities and differences between Docetaxel 20 mg/ml and Taxotere in terms of efficacy, protein binding and toxicity in non-clinical models.

These studies have been reported and are listed as follows:
• Efficacy Evaluation of Docetaxel Actavis and Taxotere Against MX-1 Human Mammary Carcinoma Xenografts.
• Efficacy Evaluation of Docetaxel Actavis and Taxotere Against PC-3 Human Prostate Carcinoma Xenografts.
• Comparative Determination of the Effect of Formulation on the Plasma Protein Binding of Docetaxel Actavis and Taxotere in Rat, Dog, and Human Plasma.
• Intravenous (Infusion) Preliminary Study in the Rat.
• Cyclical Intravenous (Infusion) Comparative Study in the Rat.
• Maximum Tolerated Dose Determination for Docetaxel Actavis in Non-Tumor Bearing Outbred Nude Mice.

No new clinical studies were conducted, which is acceptable given the legal basis of the application and that the application cross-references to a product that has been licensed for over 10 years. Since adequate quality and non-clinical data were provided to support this application, bioequivalence studies were not required.

For manufacturing sites within the Community, the RMS has accepted copies of current Manufacturer Authorisations issued by inspection services of the Competent Authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS 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.

The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP).

A change of authorisation holder was granted on 11 May 2011 to change the authorisation holder to medac Gesellschaft für klinische Spezialpräparate mbH on 11 May 2011 (PL 11587/0074).
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Taxceus 20mg/ml concentrate for Solution for Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antineoplastic agents (L01CD 02)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>20mg/ml Concentrate for Solution for Infusion</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1793/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>UK/H/1793/01/DC: Germany, Italy, the Netherlands.</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 24668/0149</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Caduceus Pharma Ltd.</td>
</tr>
<tr>
<td></td>
<td>6th Floor, 94 Wigmore Street</td>
</tr>
<tr>
<td></td>
<td>London</td>
</tr>
<tr>
<td></td>
<td>W1U 3RF</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Docetaxel
Chemical name: (2R, 3S-N-Carboxy-3-phenylisoserine, N-tert-butylester, 13-ester with 5beta, 20-epoxy-1,2 alpha 4, 7 beta, 10beta, 13 alpha-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate

Structural formula:

![Structural formula of Docetaxel](image)

Molecular formula: $C_{43}H_{53}NO_{14}$

Appearance: white to off-white powder.
Solubility: freely soluble in ethanol and tetrahydrofuran, sparingly soluble in acetonitrile, soluble in methanol, acetone and ethyl acetate and insoluble in n-hexane and water.
Molecular weight: 807.88

Docetaxel complies with in-house specifications which are in-line with those in the European Pharmacopoeia monograph for docetaxel trihydrate.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Suitable Certificates of Analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.
P. Medicinal Product

Other Ingredients
The other ingredients are the pharmaceutical excipients citric acid anhydrous, povidone, polysorbate 80 and ethanol absolute.

All excipients comply with their relevant European Pharmacopoeia monographs.

None of the excipients contain materials of animal or human origin.
No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programme was to produce products that could be considered generic medicinal products of Taxotere 20mg concentrate and solvent for infusion, first authorised in the EEA to Aventis Pharma S.A. in November 1995.

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Taxotere 20mg concentrate and solvent for infusion.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with three industrial-scale batches and has shown satisfactory results.

Finished Product Specification
The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The product is packaged in a type I colourless glass vial closed with a type I bromobutyl rubber stopper sealed with aluminium cap with polypropylene disc. Vial will be packed with or without a protective plastic overwrap.

The product will be available in the following pack sizes:
1 x 1ml single dose vial
1 x 4ml single dose vial
1 x 7ml single dose vial

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia and relevant regulations regarding use of materials in contact with food.

Stability of the product
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 24 months for an unopened product with storage conditions “Store below 25 °C” and “Store in the original package in order to protect from light”.

After the solution has been diluted, it should be used immediately after preparation. However, the
physical and chemical stability of the diluted solution (0.74mg/ml) in the recommended solutions for infusion (50mg/ml (5%) glucose solution for infusion and 9mg/ml (0.9%) sodium chloride solution for infusion) has been demonstrated for 8 hours at about 25°C and under normal lighting conditions.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPCs, PILs and labelling are pharmaceutically acceptable.

User testing results have been submitted for the PILs for these products. The results indicate that the PILs are well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

MAA forms
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
III.2 NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of docetaxel are well-known. However, it has been noted that there are differences between the proposed generic medicinal product and its respective reference product in the additional excipients present. It is for this reason that additional studies have been performed to compare efficacy, protein binding and toxicity in non-clinical models between products.

Efficacy
To determine the efficacy of Docetaxel 20 mg/ml Concentrate for solution for infusion, compared to Taxotere, established MX-1 human mammary carcinoma xenografts at a dose of docetaxel 20 mg/kg. Docetaxel 20 mg/ml and Taxotere were administered intravenously every fourth day for three treatments to female athymic (nu/nu) mice.

Treatment with either Docetaxel 20 mg/ml or Taxotere at 20 mg/kg was active and produced Day 20 T/C (median tumour mass of the treated group divided by the median tumour mass of the control group x 100) values of 0%, and tumour growth delays of >38.3 days. There were 100% complete regressions and the animals remained tumour-free at study termination. Bioanalytical analysis of plasma for both compounds on the final day of dosing confirmed similar plasma concentrations for both test articles.

The results showed that treatment with either Docetaxel 20 mg/ml or Taxotere at 20 mg/kg in terms of docetaxel content resulted in essentially identical anti-cancer activity against MX-1 human mammary carcinoma xenografts.

A further study to evaluate the anti-cancer activity of Docetaxel 20 mg/ml compared to Taxotere against established PC-3 human prostate xenografts at a dose of 20 mg/kg of the active ingredient, docetaxel, in male outbred athymic (nu/nu) mice. Docetaxel 20 mg/ml and Taxotere were administered intravenously every four days for three treatments.

Treatment with Docetaxel 20 mg/ml or Taxotere, at 20 mg/kg, was curative. It produced a Day 36 T/C value of 0%, and a tumour growth delay of >25.8 days. Treatment also produced 100% complete regressions, with all animals remaining tumour-free at study termination. Bioanalytical analysis of plasma for both compounds on the final day of dosing confirmed similar plasma concentrations of docetaxel for both test articles.

The results showed that treatment with either Docetaxel 20 mg/ml or Taxotere at 20 mg/kg in terms of docetaxel content resulted in identical anti-cancer activity against PC-3 human prostate xenografts.

Protein-binding
To determine the effect of different formulations on the degree (%) of protein binding of docetaxel, in rat, dog and human plasma in vitro, plasma protein binding determinations were made using the equilibrium dialysis technique, and samples analysed.

For the main protein binding experiments, plasma incubation samples at 1, 2.5, and 5 µg/mL were prepared in rat, dog and human plasma from five formulations of docetaxel (including the test formulation).

The time for the dialysis process to reach equilibrium when each docetaxel concentration was added to assay buffer was similar for each formulation.

The binding of docetaxel to proteins in rat, dog, and human plasma was determined, and, that within each species, there were no significant differences between the test formulation and the reference formulation.
Toxicology

To determine the maximum tolerated dose of Docetaxel 20mg/ml, upon intravenous administration every four days for three injections, a study using the substance against a vehicle control, which has the same composition as the drug product but contained no active substance was conducted. Mice were dosed according to their individual body weight on the day of the treatment (0.2ml/20g). Primary endpoints for this study were mortality, weight loss, clinical signs, skin lesions, and necropsy observations. All animals were observed for clinical signs at least once daily. Individual body weights were recorded three times weekly. Treatment-related weight loss in excess of 20% is generally considered unacceptably toxic. In this report, a dosage level is described as tolerated if treatment-related weight loss (during and two weeks after treatment) is ≤20% and mortality during this period is ≤10%. The clinical signs observed during the study and the maximum tolerated dose are similar with effects previously described for Taxotere.

In another study which was a preliminary study to determine the dose of docetaxel to use in the main study (see below), 2 male and 2 female rats were dosed once only, at a dose level of 10mg/kg docetaxel, and were then observed for 3 weeks to allow observation for delayed toxicity. All animals were observed frequently on the day of dosing, then daily for any visible signs of reaction to treatment. Body weights and food consumption were measured weekly and the animals were subjected to macroscopic necropsy at the end of the observation period.

There were no unscheduled deaths or toxicologically significant clinical changes. Bodyweight gain and food consumption values were lower for both sexes over Days 1 to 8 (the week immediately following treatment) than over Days 8 to 15 and Days 15 to 22. No abnormalities were noted at necropsy.

It was considered that 10 mg/kg docetaxel would be a suitable high dose level for the main comparative study described below.

The objective of this study was to compare the toxicity and pharmacokinetics of Docetaxel 20 mg/ml and Taxotere solutions following intravenous administration by cyclical infusion in the rat.

Table no.1 summarises the design of the study and dose levels of the active ingredient, docetaxel:

<table>
<thead>
<tr>
<th>Product and docetaxel dose level mg/kg (mg/m²)</th>
<th>Number of toxicity study animals Males Females</th>
<th>Number of toxicokinetic satellite study animals Males Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (DOCETAXEL 20 mg/ml Vehicle)</td>
<td>10 (5) 10 (5)</td>
<td>3 3</td>
</tr>
<tr>
<td>DOCETAXEL 20 mg/ml 2.5 (15)</td>
<td>10 10</td>
<td>9 9</td>
</tr>
<tr>
<td>DOCETAXEL 20 mg/ml 5.0 (30)</td>
<td>10 10</td>
<td>9 9</td>
</tr>
<tr>
<td>DOCETAXEL 20 mg/ml</td>
<td>10 (5) 10 (5)</td>
<td>9 9</td>
</tr>
<tr>
<td>Control (Taxotere® Vehicle)</td>
<td>10 (5) 10 (5)</td>
<td>3 3</td>
</tr>
<tr>
<td>Taxotere® 2.5 (15)</td>
<td>10 10</td>
<td>9 9</td>
</tr>
<tr>
<td>Taxotere® 5.0 (30)</td>
<td>10 10</td>
<td>9 9</td>
</tr>
<tr>
<td>Taxotere® 10.0 (60)</td>
<td>10 (5) 10 (5)</td>
<td>9 9</td>
</tr>
</tbody>
</table>
The toxicity study animals were sacrificed and subjected to necropsy 6 weeks after the initial dose. Animals identified in parenthesis were allocated to a 3 week recovery period following the end of the main study and necropsied 9 weeks after the initial dose.

For each subset, the dose levels examined were 0, 2.5, 5.0 and 10.0 mg/kg (equivalent to 0, 15, 30 and 60 mg/m^2) of docetaxel active ingredient. Animals were dosed twice by a 1 hour intravenous infusion at a nominal rate of 13.5 mL/kg/hr, once on Day 1 and once on Day 22. Two cycles of treatment at a three weekly interval were considered sufficient. The low dose of 2.5 mg/kg is a nominal clinical dose (approximately equivalent to 100 mg/m^2 to patients), the high dose was expected to induce toxicity, and reduced body weight gain and food consumption were observed in the preliminary study.

All formulations were accurately prepared (within 10% of nominal) and no docetaxel was found in control samples.

Six unscheduled deaths occurred during the study, none of which were considered to be related to treatment with either Docetaxel 20 mg/ml or Taxotere. There were no toxicologically significant adverse clinical signs.

Plasma concentrations of docetaxel were measurable up to 8 hours post-dose for all plasma samples for the higher two dose levels and for the majority of plasma samples for the 2.5 mg/kg dose level. This indicates almost continuous exposure of the rats to docetaxel up to 8 hours post-dose at all dose levels. The apparent Tmax generally occurred at 5 minutes post-dose, however this is an underestimate of the actual Tmax. Plasma concentrations of docetaxel declined with mean terminal half-lives, where calculable, in the range 140 minutes to 216 minutes.

Peak levels and systemic exposure increased from the 2.5 mg/kg to the 5 mg/kg dose levels in an approximately dose proportional manner. However, the increase in systemic exposure data showed an approximate 1.5-fold increase greater than the dose level increase for both Day 1 and Day 22 data for the 10.0 mg/kg dose groups. These parameters are compared in table no. 2.

<table>
<thead>
<tr>
<th>Test article</th>
<th>Docetaxel Actavis</th>
<th>Taxotere®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level</td>
<td>2.5 mg/kg</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>53.2</td>
<td>53.4</td>
</tr>
<tr>
<td>AUC0-8 (ng.mins/mL) Day 1</td>
<td>5680</td>
<td>4580</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 22</td>
<td>68.7</td>
<td>66.7</td>
</tr>
<tr>
<td>AUC0-8 (ng.mins/mL) Day 22</td>
<td>7660</td>
<td>4100</td>
</tr>
</tbody>
</table>

Generally, there appeared to be no consistent differences between sexes for the peak levels of docetaxel or the systemic exposure on Day 1. On Day 22, the male rats showed a small but consistent increase (less than 2-fold) in both peak levels and the systemic exposure of docetaxel. Where calculable, clearance and volume of distribution were slightly higher in females, consistent with the lower levels of
exposure in the females on Day 22. The extent of systemic exposure following a second administration was similar compared to a single administration. Clearance and volume of distribution values, where calculable, were generally similar following the second dose. Overall, there was little accumulation potential of docetaxel following a second administration.

There were neither major nor consistent differences for the peak levels or the systemic exposure of docetaxel following dosing with either Docetaxel 20 mg/ml or Taxotere.

It is concluded that the toxicological profile based on evaluation of body weight gain, food consumption, ophthalmic examination, haematology and bone marrow smears, clinical chemistry, urinalysis, organ weights, gross and histopathology and toxicokinetic profiles of Docetaxel 20 mg/ml and Taxotere, following 2 cycles of intravenous infusion dosing, 3 weeks apart, at dose levels of 2.5, 5.0 or 10.0 mg/kg docetaxel, were comparable. Administration of either product resulted in changes consistent with the known toxicity of the active ingredient docetaxel.

This study showed that there were no major or consistent differences in the toxicological profiles of the test product versus the reference product.

These studies show:
1. Treatment with Docetaxel 20 mg/ml and Taxotere at 20mg/kg in terms of docetaxel content resulted in identical anti-cancer activity against both the MX-1 and PC-3 xenografts following intravenous administration every four days for three treatments.
2. The clinical signs observed in the study and the maximum tolerated dose were similar to those previously described for Taxotere.
3. The developed drug product pharmacokinetics properties were essentially comparable with reference product in terms of toxicokinetics.

All non-clinical studies were conducted in accordance with Good Laboratory Practice (GLP).

The non-clinical overview has been written by an appropriately qualified physician and is adequate.

A suitable justification has been provided for non-submission of an Environmental Risk Assessment.

There are no objections to the approval of Taxceus 20mg/ml concentrate for solution for infusion from a non-clinical point of view.

III.3 CLINICAL ASPECTS
1. Introduction
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports
As per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98 in force at the time of application, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product.

However, the product contains micelles and micelle solutions for IV administration may be regarded as ‘complex’ solutions and therefore do not automatically qualify for a biowaiver. To address this issue, the quality/physicochemical properties of the proposed product were shown to be comparable with the
reference product by the provision of adequate quality and non-clinical data. Therefore, no further clinical studies were required.

3. **Post marketing experience**
Docetaxel has a well-recognised efficacy and an acceptable level of safety in the indications approved for Taxotere 20mg concentrate and solvent for infusion, and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the Marketing Authorisations is supported.

4. **Benefit-Risk assessment**
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with docetaxel is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

5. **Conclusions**
The grant of a Marketing Authorisation for Taxceus 20mg/ml concentrate for solution for infusion is recommended from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Taxceus 20mg/ml concentrate for solution for infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
Due to differences between the proposed medicinal product and the reference product with regards to additional excipients, additional studies have been performed to compare efficacy, protein binding and toxicity between products in non-clinical models between products. These studies support the claim that the product can be considered equivalent to the reference product.

CLINICAL
No bioequivalence studies have been performed and none are required for this application, since adequate quality and non-clinical data have been provided.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with docetaxel is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
**Module 6**

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 July 2013</td>
<td>II</td>
<td>To update section 1 (Name of the medicinal product), 2 (Qualitative and quantitative composition), 4 (Clinical particulars), 5 (Pharmacological properties), 6 (Pharmaceutical properties) of the SmPC in line with the QRD template, brand leader and also following the literature review. The leaflet and label is updated consequently</td>
<td>Granted 24 January 2014</td>
</tr>
</tbody>
</table>
ANNEX 1  
CLINICAL VARIATION ASSESSMENT REPORT

Reason:
To update section 1 (Name of the medicinal product), 2 (Qualitative and quantitative composition), 4 (Clinical particulars), 5 (Pharmacological properties), 6 (Pharmaceutical properties) of the SmPC in line with the QRD template, brand leader and also following the literature review. The leaflet and label is updated consequently.

Recommendation
Based on the review of the information provided by the Applicant, the RMS considers that the group of variations for Taxceus (Docetaxel), in the treatment of cancer, for the following proposed changes:

- Type IB C.I.z: Update of product information in line with QRD template
- Type IB C.I.z: Editorial update of SmPC section 6.3 Shelf life
- Type IB C.I.2.a: Update of product information in line with the reference product Taxotere
- Type II C.I.3.b: Update of SmPC section 4.8. Undesirable effects, to amend a term of subsection Post-Marketing Experience and consequential PL changes

Is approvable
The MAH is requested to update the product information in line with the innovator product, after the discussion regarding a grapefruit warning has been agreed.

Executive Summary

Scope of the variation
The Applicant has submitted the group variations, concerning safety and QRD template changes. The changes are acceptable.

Scientific discussion

Quality aspects
N/A

Non clinical aspects
N/A

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Clinical pharmacology
N/A

Clinical efficacy
N/A

Clinical safety
Evidence to support variation
The clinical overview states that ‘this is an update of the Clinical Overview for Taxceus 20 mg/ml concentrate for solution for infusion (MA number UK: PL 11587/0074) intended to adapt the medicinal product labelling according to the most actual Summary of Product Characteristics (SmPC) of the Reference Product (TAXOTERE,
As the SmPC of the reference product has been changed, this grouped variation procedure has been conducted to include the safety relevant information into the label of Taxceus 20 mg/ml concentrate for solution for infusion. Following a review of literature reports a term of subsection Post-Marketing Experience in section 4.8. (Undesirable effects) is amended.

The Applicant also submits with the application a letter from the MHRA which states: The Pharmacovigilance Risk Assessment Committee (PRAC) reviewed two well documented literature cases of clinically significant pharmacokinetic drug interactions between docetaxel and CYP3A4 inhibitors (grapefruit juice, dronedarone) resulting in increased docetaxel toxicity (neutropenia, mucositis).

**Post marketing experience**
The clinical overview details literature reports regarding the so called ‘recall phenomena’. In order to better inform prescribers, the Applicant proposes the following changes:

Current: Radiation recall phenomena have rarely been reported.

Amended to:

Proposed: Recall phenomena including radiation recall, injection site recall and sunburn recall have rarely been reported.

**Product information**

**Summary of Product Characteristics**
The changes are acceptable.

**Package leaflet and user test**
The changes are acceptable.

**Labelling**
The changes are acceptable.

**Overall Conclusion and Benefit-risk assessment**
The proposed changes to the product information are considered to be acceptable. The changes do not alter the benefit risk profile.

**Request for supplementary information as proposed by the RMS**

**Potential serious risks to public health**
None

**Points for clarification**
None
Summary of Product Characteristics
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Labelling