Doc. Ref.:EMA/CHMP/110616/2010
Evaluation of Medicines for Human Use

Assessment Report

Docefrez

International Nonproprietary Name: docetaxel

Procedure No. EMEA/H/C/001074

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Sun Pharmaceutical Industries Europe B.V. submitted on 02 October 2008 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Docefrez in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) No 726/2004 under Article 3(3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to: Article 10(3): hybrid application.

The chosen reference product is:

■ *Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:*

- Product name, strength(s), pharmaceutical form(s): **Taxotere, 20 mg/0.5 ml and 80 mg/2 ml, Concentrate and solvent for solution for infusion**
- Marketing authorisation holder: **Aventis Pharma S.A.**
- Date of authorisation: **27 November 1995**
- Marketing authorisation granted by: **Community**
- Marketing authorisation number: **EU/1/95/002/001-002**

■ Medicinal product which is or has been authorised in accordance with Community provisions in force:

- Product name, strength, pharmaceutical form: **Taxotere, 20 mg/0.5 ml and 80 mg/2 ml,**
  Concentrate and solvent for solution for infusion
- Marketing authorisation holder: **Aventis Pharma S.A.**
- Date of authorisation: **27 November 1995**
- Marketing authorisation granted by: **Community**
- Marketing authorisation numbers: **EU/1/95/002/001-002**
- Bioavailability study number(s): **Not applicable**

■ Medicinal Product which is or has been authorised in accordance with Community provisions in force used in other studies (where applicable)

- Not applicable

The Rapporteurs appointed by the CHMP were:

Rapporteur :	Dr. Robert James Hemmings
Pharmacovigilance Rapporteur :	Dr. Pierre Demolis

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

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

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 02 October 2008.
- The procedure started on 22 October 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 09 January 2009. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 16-19 February 2009, 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 20 February 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 July 2009.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 09 September 2009.
- During the CHMP meeting on 21-24 September 2009, the CHMP agreed on a List of Outstanding Issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 16 November 2009.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 November 2009, and the updated version on 03 December 2009.
- During the CHMP meeting on 14-17 December 2009, the CHMP agreed on a 2nd List of Outstanding Issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated 2nd List of Outstanding Issues on 11 January 2010.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 02 February 2010.
- During the meeting on 15-18 February 2010, 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 Docefrez on 18 February 2010.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Docefrez powder and solvent for concentrate for solution for infusion is a medicinal product containing docetaxel as active substance. Two strengths have been developed, 20 mg and 80 mg. The reference medicinal product Taxotere concentrate and solvent for solution for infusion has been centrally authorised since 27 November 1995 and is at present available in the following strengths; 20 mg/0.5 ml, 80 mg/2 ml, 20 mg/1 ml and 80 mg/4 ml. In this EPAR only reference to Taxotere strengths 20 mg/0.5 ml and 80 mg/2 ml is made. The active substance in Docefrez and Taxotere is the same, docetaxel. Docefrez contains docetaxel in the anhydrous form, whereas Taxotere contains docetaxel as a trihydrate. Docefrez is a hybrid medicinal product in the sense that the pharmaceutical form is different compared to the reference medicinal product. Docefrez 20 mg and Docefrez 80 mg are hybrids of Taxotere 20 mg/0.5 ml (EU/1/95/002/001) and Taxotere 80 mg/2 ml (EU/1/95/002/002), respectively. Docefrez is presented as a package containing one powder and one solvent vial whereas a package of the reference medicinal product contains one concentrate and one solvent vial.

Similar to the reference product, the Docefrez powder vial needs to be reconstituted with the solvent vial before dilution into the infusion bag. The qualitative composition of the reconstituted solution (premix) is similar for both products, but the quantitative composition is different. After reconstitution of the 20 or 80 mg strength, the Docefrez premix contains 24 mg/ml docetaxel whereas the Taxotere premix contains 10 mg/ml docetaxel.

The medicinal product Docefrez is intended for intravenous administration after reconstitution and dilution in an infusion bag containing either 5% glucose solution or 0.9% sodium chloride solution. Reconstitution occurs by withdrawing the content of the solvent vial with a syringe and injecting the solvent into the powder vial as explained in the package leaflet.

Docefrez is indicated in the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, head and neck cancer. The indications of Docefrez are the same as for the reference medicinal product (see page 19).

2.2 Quality aspects

Introduction

The medicinal product Docefrez contains the active substance docetaxel and is presented as powder and solvent for concentrate for solution for infusion. Docefrez is available in two strengths 20 mg and 80 mg. A Docefrez package contains two vials, one powder vial and one solvent vial.

The powder vial contains a white sterile lyophilised cake intended for reconstitution with the solvent provided in the separate solvent vial. The powder vial contains only the active substance docetaxel and no excipients. The powder is packed into colourless glass vials with grey rubber closures and sealed with flip-off aluminium seals (dark green for 20 mg, blood red for 80 mg).

The solvent vial contains polysorbate 80 and anhydrous ethanol and is used to dissolve the powder. The solvent is a viscous, clear, colourless, sterile solution and is packed into colourless glass vials with grey rubber stoppers sealed with flip-off aluminium seals (dark blue for 20 mg, brown for 80 mg).

Active Substance

The chemical name for docetaxel is (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.
The molecular formula is $C_{43}H_{53}NO_{14}$ and the molecular weight is 807.88 g/mol. Docetaxel is a white to off-white powder, which is highly hygroscopic and highly lipophilic. At 25 °C, docetaxel is freely soluble in ethanol and tetrahydrofuran, soluble in methanol, acetone and ethyl acetate, sparingly soluble in acetonitrile and insoluble in n-hexane and water. There is no Ph.Eur. monograph for anhydrous docetaxel, however a Ph.Eur. monograph exists for docetaxel trihydrate.

Docetaxel has eleven chiral centres and one stereoisomer, epi-docetaxel (7-epi-docetaxel). Docetaxel exhibits polymorphism. The manufacturing conditions have been chosen to ensure that docetaxel is always produced as a single crystalline morphological form. It is noted that the active substance used in the reference medicinal product is the trihydrate form. However given that both medicinal products aim to deliver the active substance in solution, the active substance in Docefrez and in the reference medicinal product are considered equivalent.

The chemical structure of docetaxel has been confirmed by elemental analysis, ultra-violet (UV) spectra, infrared (IR) spectra, mass spectra and nuclear magnetic resonance (NMR). All data are consistent with the proposed structure.

- Manufacture

The manufacture of docetaxel consists of an eight-step process. Detailed information about the manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates and process development and process validation of the active substance has been supplied in the form of an active substance master file (ASMF). At the time of the opinion, only one active substance manufacturer is used. All manufacturing steps are adequately described. Adequate in-process controls are in place and appropriate specifications have been adopted for the starting materials, solvents and reagents. All relevant impurities, degradation products and residual solvents have been appropriately characterised.

- Specification

As for anhydrous docetaxel no monograph exists in the Ph. Eur. or USP, in-house specifications have been set for the active substance, in accordance with the principles of ICH guidelines. The specification has been harmonised to the Ph.Eur. monograph for docetaxel trihydrate where possible. The active substance specifications of the MAH are the same as those of the active substance manufacturer.
The active substance specifications include appropriate tests for appearance, identifications (IR spectra and HPLC), assay and related substances (HPLC), residual solvents (GC), water content (Karl Fischer and coulometry), specific optical rotation, heavy metals, bacterial endotoxins, microbial limit and residue on ignition/sulphated ash.
The analytical procedures have been satisfactorily described and validated in accordance with the ICH guidelines. The impurity limits are acceptable and there is no concern from the point of view of safety. Batch analysis data and Certificates of Analysis have been presented and all batches were in compliance with the predefined active substance specification.

- Stability

Stability studies have been performed in accordance with the ICH requirements for substances intended to be stored under refrigeration. Long-term stability data (at 5 ± 3°C, 60 ± 5% RH) and accelerated stability data (at 25 ± 2 °C/60 ± 5 % RH) have been provided for four pilot scale batches of the active substance. In addition to this, forced degradation studies were performed to determine the stability of the active substance at 4, 25, 50 and 75 °C for 4 weeks in different environments. Furthermore, studies were performed to determine the stability of the active substance in oxygen and nitrogen at various temperatures (25, 50 or 75 °C during 4 weeks) and to determine the stability of the active substance in solution at pH 2, 5 and 7 at various temperatures. In addition, a photostability study was also performed in line with ICH Q1B, which indicated that the active substance is slightly photosensitive in the solid state and very photosensitive in solution form.
The test parameters evaluated in these studies were appearance, specific rotation, assay, purity, residual solvents, water content, bacterial endotoxins and microbial count. The packaging used in stability trials is identical to that proposed for market. The stability data provided justify the proposed retest period at the proposed storage conditions.

Medicinal Product

- Pharmaceutical Development

The medicinal product Docefrez 20 mg and 80 mg powder and solvent for concentrate for solution for infusion is a generic (hybrid) version of the reference medicinal product Taxotere concentrate and solvent for infusion 20 mg/0.5 ml and 80 mg/2 ml, respectively.

The aim of the pharmaceutical development was to develop a generic (hybrid) medicinal product that contains the same active substance (but in a different hydrate form) and that is intended for the same indications, dosage regimens and route of administration as the reference medicinal product Taxotere, without infringement upon composition patents held by the innovator company. Two strengths of Docefrez have been developed; 20 mg and 80 mg, both having a very similar qualitative composition compared to the reference product.

Docefrez differs from the reference medicinal product with respect to pharmaceutical form of the finished product and the hydrate form of the active substance. Taxotere contains docetaxel trihydrate and the active substance is presented as a concentrate in polysorbate 80 intended for dilution in ethanol in water for injections (solvent provided in a separate vial) prior to subsequent dilution in a suitable infusion solution. Docefrez contains anhydrous docetaxel and is presented as a powder and solvent for concentrate for solution for infusion. The powder vial contains docetaxel and the solvent vial contains polysorbate 80 and anhydrous ethanol. Docefrez contains more ethanol than the reference medicinal product. The higher ethanol content in Docefrez is considered not relevant as Docefrez is to be diluted into an infusion bag before administration to the patient. The concentration of docetaxel in the reconstituted (premix) solution is also different for Docefrez and the reference medicinal product. After reconstitution, Taxotere 20 and 80 mg results in a 10 mg/ml premix, whereas Docefrez 20 and 80 mg results in a 24 mg/ml docetaxel premix solution. The docetaxel concentration in the reconstituted (premix) solution is adequately reflected in the SmPC, PL and preparation guide for health care professionals.

By applying overfill on the powder vial, it is ensured that the volume which is extracted from the premix solution contains the appropriate amount of docetaxel. For the 20 mg strength, the minimal extractable volume from the premix solution is 0.84 ml containing 20 mg docetaxel (anhydrous). For the 80 mg strength, the minimal extractable volume from the premix solution is 3.36 ml containing 80 mg docetaxel (anhydrous). This is reflected in the SmPC and preparation guide.

During development, the MAH focussed mainly on obtaining a stable and sterile formulation. In the stability studies, the MAH demonstrated compatibility of the active substance with the excipients. All of the excipients are used commonly in parenteral products and stability data are considered acceptable. Adequate compatibility studies have been performed to show compatibility and stability of the premix and after dilution with the infusion solutions proposed in the SmPC.

Docefrez is to be administered as a non-aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference product Taxotere (following reconstitution) at the point of administration. The Note for Guidance on the Investigation of Bioavailability and Bioequivalence, (CPMP/EWP/QWP/1401/98), states that 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 this is a non-aqueous solution and no specific guidance is given. The MAH provided reports of several *in vitro* pharmaceutical studies and two non-clinical studies to compare the proposed Docefrez product with the reference product, Taxotere. All of these studies support the claim that the proposed product is equivalent pharmaceutically to the reference product and therefore that the proposed biowaiver is acceptable.

- Adventitious Agents

No component of human or animal origin is used for the finished product manufacture; therefore there is no BSE/TSE risk. BSE/TSE declarations from the active substance manufacturer and the manufacturers of the excipients are provided.

- Manufacture of the Product

The manufacturing process of Docefrez has been confirmed as a two-step filling process and has been adequately described and validated. All critical process parameters have been identified and are controlled by appropriate in-process controls. The manufacturing process is demonstrated to be

reproducible and provides a finished product that complies with the in-process and finished product specifications.

- Product Specification

The medicinal product specifications for Docefrez at batch release include the following tests on the powder vial: tests for description, identification (HPLC and IR), water content, reconstitution time, uniformity of dosage units, visual inspection, transmittance and absorbance of the constituted solution, related substances, residual solvent (ethanol), assay, particulate matter, sterility and bacterial endotoxin. The specifications for the solvent vial include tests for: description, ethanol identification and content, transmittance and absorbance of the solvent, volume in container and volume variation, particulate matter, sterility and bacterial endotoxins. All tests included in the specification have been satisfactorily described and validated. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. All excipients used in the formulation comply with the monographs of the current Ph.Eur. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. Batch analysis results comply with the proposed specification and confirm consistency and uniformity of manufacture and indicate that the process is under control.

- Stability of the Product

Stability studies have been carried out under long term (5 ± 3 °C) and accelerated (25 ± 2 °C/60 ± 5 % RH) conditions according to the ICH requirements. Long term stability data up to 36 months and accelerated stability data up to 6 months have been provided. All batches placed on stability studies were manufactured at the proposed site of finished product manufacture, according to the proposed process and using active substance obtained from the proposed active substance manufacturer. All batches were packaged as proposed for marketing. The parameters tested and analytical methods used were identical to those used for the release specifications. However, some release tests were not repeated at the end of shelf-life. Furthermore, a photostability study was performed on one batch of the 80 mg presentation, in accordance with ICH Q1B and at 25 ± 2 °C.
The stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SmPC. The MAH confirmed that the first three batches of both strengths (20 mg and 80 mg) will be placed on stability trials in line with the ICH guidance to confirm the shelf-life. In accordance with GMP, the MAH confirmed to investigate any out of specification result in stability data and report any such result to the competent authorities.

Discussion on chemical, and pharmaceutical aspects

The quality of Docefrez is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. There are no major deviations from EU and ICH requirements.

Information on the development, manufacture and control of the active substance and drug product has been presented in a satisfactory manner. The results of batch testing indicate satisfactory consistency and uniformity of product quality characteristics and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

Docefrez is a hybrid medicical product, meaning that the pharmaceutical form is different from the reference medicinal product; Taxotere. The qualitative composition is very similar; however the quantitative composition with respect to the excipients is different from Taxotere. It is noted that Docefrez contains more ethanol than Taxotere. In addition, the docetaxel concentration of the premix solution obtained after reconstitution is different from the reference medicinal product. This was determined to be acceptable considering that the volume of Docefrez premix solution that can be extracted from the vial after reconstitution of the Docefrez 20 mg (or 80 mg) presentation contains 20 mg docetaxel (or 80 mg respectively).

The CHMP concluded that the observed differences between Docefrez and Taxotere are minor and are not considered to be clinically relevant. At the time of the CHMP opinion, there were no unresolved quality issues having impact on the benefit/risk ratio of the product.

2.3 Non-Clinical aspects

The Applicant has submitted a non-clinical overview which is based on a literature review including 32 publications up to 2008. In addition three non-clinical studies have been submitted: a pharmacology study (comparative efficacy vs. reference product in mice), a pharmacokinetic study (comparative plasma concentration study in the rat) and a toxicological study (comparative acute toxicity study in mice of docetaxel containing the 7-epimer impurity and Taxotere). All submitted studies were conducted in compliance with the principles of GLP.

Pharmacology

Mechanism of action

Docetaxel is an antineoplastic agent which acts by promoting (rate and extent) the assembly of tubulin into stable microtubules and inhibits their disassembly preventing their depolymerization. The consequences of blocking microtubule dynamics are complex: a number of vital cellular functions in which microtubules play a critical role are compromised. Impairment of mitotic progression leading to cell cycle arrest is considered to be a principal component of docetaxel's mechanism of action. This blocks progression of a cell through its natural division cycle, and consequently, inhibits cell proliferation.

Docetaxel produces changes in cell shape including alteration of the cytoskeleton morphology. It was found that the amount of tubulin was increased in KB 3-1 human epidermoid carcinoma cells treated by both paclitaxel and docetaxel before the accumulation of cells in the G2/M phase. Docetaxel leads to the formation of bundles and asters in KB 3-1 cells and in J82 human bladder carcinoma cells, and accumulates cells in the G2/M phase leading to an inability of the cells to divide. In HeLa synchronised cells, docetaxel and paclitaxel are active during the S phase. Docetaxel does not inhibit synthesis of DNA, RNA or protein using P388 leukemia cells. Higher potency of docetaxel observed *in vitro* may be explained by the combination of its higher affinity for microtubules, its higher achievable intracellular concentration and the slower cellular efflux. Docetaxel primarily targets centrosome organisation, leading to abortive mitosis and cell death. *In vitro* it is almost totally lethal to cells exposed during S phase, with only partial toxicity against cell sin mitosis and this declines to a minimum with progression to G1. Exposure during S phase does not delay progression to G2 but leads to gross damage after mitosis with dysfunction in cytokinesis and accumulation of multinucleated, non-viable cells.

Disruption of microtubules not only affects progression through the cell cycle, but may also alter signalling pathways involved in processes such as apoptosis and docetaxel has been reported to promote apoptosis in cancer cells. Several signal transduction pathways may be involved in docetaxel's effects on apoptosis and the *Bcl*-gene family in particular appears to play a critical role in the regulation of apoptosis. Inhibition of Bcl-2 induces apoptosis, whereas overexpression of Bcl-2 prevents or delays apoptosis (enhancing cell survival) and may be a factor relating to chemotherapeutic drug resistance. Consequently, down regulation of Bcl-2 expression has been investigated as a strategy for reversal of resistance. Antimicrotubule agents are believed to cause inactivation of Bcl-2 function through phosphorylation.

Epidermal growth factor receptor (EGFR) signalling pathways present one of those that feed into processes affected by docetaxel, that is, apoptosis and angiogenesis. Members of the EGFR family (e.g., the human epidermal growth factor receptors HER-1 and HER-2) and their signalling pathways influence cell cycle regulation, angiogenesis, and apoptosis. Signals are transmitted from the cell surface to the cell nucleus via a variety of downstream effector proteins such as Ras and MAP kinase. HER-1 is overexpressed in a wide range of tumours, especially SCCHN, where it is associated with poor prognosis. HER-2 is also overexpressed in many tumour types, in particular, breast cancer (30% of tumours). HER-2 overexpression imparts a metastatic advantage to the cell and is associated with impaired survival in the patient.

Tumour angiogenesis is a critical component of tumour growth and metastasis and targeting of the vascular supply of tumours is an intense field of interest, with many promising preclinical trials highlighting the potential effectiveness of this form of therapy. Endothelial cell migration and proliferation are key components of tumour angiogenesis, and agents that target the microtubule cytoskeleton can interfere with these processes. It has been demonstrated that docetaxel inhibits endothelial cell migration and angiogenesis *in vitro* and *in vivo*. *In vitro* this was achieved at concentrations substantially below those that inhibited the proliferation of the cells or caused alterations in their shape or viability. The effects of docetaxel on migration were associated with a reduction in the reorientation of the cell's centrosome, at concentrations that did not affect gross microtubule morphology or proliferation. Results of these *in vitro* studies demonstrate that

endothelial cell migration correlates more closely with changes in microtubule plasticity than with microtubule gross structure. *In vivo*, angiogenic response to fibroblast growth factor 2 was inhibited *in vivo* by docetaxel with an ID50 of 5.4 mg/kg when injected twice weekly over a 14-day period, and angiogenesis was completely blocked in mice that received 10 mg/kg docetaxel. *In vivo* data further suggested that docetaxel had selectivity for endothelial cell migration and/or microvessel formation because infiltration of inflammatory cells into the Matrigel plug was much less sensitive to inhibition by docetaxel. Thus, docetaxel is a potent and potentially specific inhibitor of endothelial cell migration *in vitro* and angiogenesis *in vitro* and *in vivo*. The antiangiogenic effect of docetaxel is four times stronger than that of paclitaxel and enhancement of antiangiogenic properties of docetaxel through inhibition of endogenous angiogenic growth factors such as vascular endothelial growth factor (VEGF) demands further investigation.

Primary pharmacodynamic studies

Docetaxel has been shown to have significant inhibitory activity against cell lines P388 (murine leukaemia), KB (epidermoid carcinoma), CEM (acute lumphoblastic leukaemia), N417 (small-cell lung carcinoma), and 24 (bladder carcinoma). It also has *in vitro* cytotoxicity in murine (P388, SVras) and human cell lines (Calc18, HCT116, T24, N417, and KB). Docetaxel's activity against freshly explanted human tumour cells has been demonstrated. Breast, lung, ovarian, and colorectal cancers and melanomas have also been found to be responsive to docetaxel. It has a lesser degree of activity against Lewis lung carcinoma, Glasgow osteogenic sarcoma and the L1210 and P388 leukemias. Docetaxel is reported to have a significant concentration-dependent effect on the frequency of growth-inhibition in breast cancer, non-small cell lung cancer, melanoma, ovarian cancer, and colorectal cancer.

Docetaxel is thus cytotoxic against both murine and human tumour cell lines *in vitro*, with the latter being most drug sensitive. The concentration of docetaxel required to reduce cell survival by 50% (IC50) ranged from 4 to 35 ng/ml, and the cytotoxic effects were greater on proliferating than non-proliferating cells, being both time- and concentration-dependent. The AUC values required for 50% kill of tumour cells *in vitro* were much lower (0.4-3.4 µg/ml.h) than the pharmacologically achievable AUC values in mice at non-toxic dosage both in plasma (17 µg/ml.h) and in tumour (44 µg/ml.h). Thus, docetaxel achieves concentrations in plasma and tumours which are much greater than is required for 50% kill of tumour cells.

Docetaxel's *in vivo* antitumour activity was investigated using transplantable tumours and found to have wide spectrum efficacy. It was highly active against B16 melanoma model (producing a total log-cell kill of 3, which is 2.7 times greater than that achieved with paclitaxel in the same system) and against pancreatic ductal adenocarcinoma 03 and colon adenocarcinoma 38, producing total 100% cures in early-stage disease and greater than 80% complete regressions in advanced-stage disease. Colon adenocarcinoma 51/A, early and advanced stages, was also highly sensitive to docetaxel, while other cell lines were less responsive.

Docetaxel is active against three colon tumours. The most responsive is the 5-FU sensitive colon 38 with 100% cure rate of early stage disease, and complete regressions of advanced stage tumours. It is also active against the slow-growing, mucin-producing, adenocarcinoma colon 51 at both early and advanced stage. Modest activity was found against the undifferentiated colon adenocarcinoma 26. Pancreatoc ductal adenocarcinoma is another tumour very sensitive to docetaxel.

Docetaxel has been shown active against several murine breast cancer cell lines*:*
- Mice bearing early stage MA16/C (fast growing metastatic adenocarcinoma) tumours were treated using a 2 days x 3 schedule. At the highest non-toxic dose (15 mg/kg/injection), docetaxel was found to be highly active with a 0% T/C value corresponding to a 2.4 log cell kill. Against advanced stage MA16/C (tumour burden ranging from 126 to 395 mg, with a median of 190 mg) using the same schedule. The highest non-toxic dose was 10.8 mg/kg/injection, and produced 100% complete regressions.
- Docetaxel was administered on an every 2 days x 3 schedule to mice bearing early stage MA13/C tumours. The highest non-toxic dose (14.2 mg/kg/injection) produced a 0% T/C value with a 4.3 log cell kill. At an advanced stage (tumour burden ranged from 200 to 320 mg), the highest non-toxic dose (15 mg/kg/injection), administered on an every 3 days x 3 schedule, yielded 60% complete regressions with a 2.5 log cell kill.
- At the highest non-toxic dose (15 mg/kg/injection), administered on days 4, 6 and 8 post-tumour implantation of mammary 17/A cells, docetaxel was found to be highly active, with a 0% T/C value

and a 2.8 log cell kill.
- At the highest non-toxic dose (22 mg/kg/injection), the T/C value indicated very minor docetaxel activity on mammary adenocarcinoma 44, which has marginal sensitivity to doxorubicin.
- For the mammary adenocarcinoma 17/A, doxorubicin is highly sensitive to the parent tumour MA17/A. The resistant tumour MA17/A/Adr is 4-fold less sensitive based on log cell kill. At the highest non-toxic dose, docetaxel (22.5 mg/kg/injection) was found to be cross-resistant with MA17/A/Adr, with a 74% T/C value.
- A slow growing adenocarcinoma, it was established in mice using 10^7 cells per mouse, and was then propagated was found to be highly active on palpable Calc18 and yielded a 2.1 log cell kill at the highest non-toxic dose. The mammary MX-1 cell line is a carcinoma that is sensitive to L-Pam. The highest non-toxic dose of docetaxel produced 100% complete regressions of tumours that weighed approximately 320 mg when treatment was initiated. There was no recurrence up to 84 days posttumour implantation.

In order to support the claim that the differences in formulation of the proposed and reference products do not impact on the behaviour of the product the Applicant submitted an *in vivo* study comparing the efficacy of Docefrez versus the reference product Taxotere. The model used was based on a human mammary carcinoma xenograph in athymic nude mice. Docefrez was administered in tumour bearing mice at a dose of 15mg/kg with a dosing regimen of 3 repeated injections (day 0, 4 and 8). The results indicate that both Docefrez and Taxotere showed antitumour activity at the end of the 38 day study. The efficacy and toxicity profile of Docefrez was comparable to the reference product.

Pharmacodynamic drug interactions

In combination chemotherapy, choice of agents was guided by the clinical activity observed in phase II trials in breast, ovarian, and lung tumours: doxorubicin (breast), 5-fluorouracil (breast), cyclophosphamide (breast, lung, ovarian), cisplatin (ovarian, lung), etoposide (small cell lung cancer), vinca alkaloids (breast lung), methotrexate (breast), and mitomycin C (lung). When selecting agents it is standard practice to combine agents with different mechanisms of action.

In *in vivo* studies of mice bearing s.c. transplanted tumours, certain combinations of docetaxel with other antitumour agents produced a modest to marked synergistic effect with: vincristine (against P388), vinorelbine (against MA16/C), navelbine, etoposide (against B16 melanoma), cyclophosphamide (against MA13/C), mitomycin C (against MA13/C) and 5-FU (against colon 38).

Synergistic effects have been noted with docetaxel and cyclophosphamide against MA13/C mammary adenocarcinoma with a 33% cure rate. These agents have different mechanisms of action and have been proven not to demonstrate cross-resistance or is only partial *in vivo* on B16 melanoma. But cross resistance was noted *in vitro* using a P388/Adr cell line and using an in vivo mammary adenocarcinoma resistant to doxorubicin (MA17/A/Adr). However, absence of cross-resistance was shown using cells that expressed low levels of vincristine or etoposide resistance, but which were P-glycoprotein positive, and previously cited Susa/VPC3 and Susa/VPC4, indicating that *in vitro* cross-resistance was not automatically observed in sublines expressing the multidrug resistance phenotype.

The combination of docetaxel and etoposide also demonstrated therapeutic synergism against B16 melanoma. Furthermore, absence of cross-resistance was also observed both *in vivo* in the B16 melanoma model resistant to docetaxel and in two *in vitro* cell lines selected for low levels of etoposide resistance.

The combination of trastuzumab with docetaxel against four HER-2 overexpressing breast cancer cell lines resulted in combination index values ranging from 0.30 (95% CI = 0.04 to 0.56; $p<0.001$) in SK-BR-3 cells to 0.62 (95% CI = 0.29 to 0.95; $p<0.001$) in MDA-MB-453 cells, indicating synergism. Cell lines with higher HER-2 levels (SK-BR-3 and BT-474) had lower combination index values than cell lines with lower HER-2 levels, indicating enhanced synergy against tumour cell with higher HER-2 overexpression. Further to these *in vitro* results, the combination had statistically significant increased antitumour efficacy *in vivo* against MCF-7/HER2-overexpressng xenografts compared with either single agent alone, and there was an increase in

durable complete responses in mice treated with docetaxel plus trastuzumab compared with mice treated with either single agent alone.

In terms of toxicity, the combination toxicity index (CTI, the sum of the fractions of the LD10 of each agent) ranged from 0.75 for the most toxic combination (docetaxelcisplatin), indicating complete overlap in dose-limiting toxicity, to a CTI index of 2 for the least toxic combination, docetaxel-vincristine (simultaneously administered). Thus, the maximum tolerated dose of each agent could be administered without additional toxicity. The most aggressive combinations were found to be docetaxel cisplatin and docetaxel-mitomycin C. The optimal doses of each agent that could be administered in the highest non-toxic combinations were 43% and 50%, respectively. But it should be noted that there was no hyperhydration for the docetaxel-cisplatin combination which is a deviation to standard clinical practice.

The vinca alkaloids share the same target, that is, tubulin-microtubule system, either inhibiting tubulin polymerisation in the case of the vinca alkaloids or inhibiting microtubule depolymerisation in case of taxoids.

Dexamethasone was administered s.c. simultaneously with docetaxel i.v. every 2 days for 3 injections in mice bearing s.c. B16 melanoma. Dexamethasone (0.5 mg/kg/dose) dose was the highest that could be administered safely on a chronic schedule (8.6% body weight loss). Docetaxel administered as a single agent produced 15.3% body weight loss and 2.0 log cell kill at the highest non-toxic dose (20 mg/kg/injection). The highest non-toxic dose of docetaxel using the dexamethasone/docetaxel concomitant regimen was unchanged (20 mg/kg/injection). This combination produced a 16.7% body weight loss at nadir, and thus premedication to prevent hypersensitivity reactions did not influence the maximum tolerated dose and the efficacy was similar at all the dose levels tested.

Resistance

Resistance to the cytotoxic actions of docetaxel may occur owing to alterations in tubulin or increased expression of the multidrug-resistant gene and subsequent overproduction of the P-glycoprotein.

Acquired resistance to taxoids *in vitro* is likely either due to multidrug resistance phenotype related to overproduction of P-glycoprotein, or that due to tubulin alteration. Human breast adenocarcinoma cells resistant to docetaxel (Calc18/TXT), which overexpress the MDRI gene and have decreased β-tubulin mRNA levels compared with parental cells, are 15 times less sensitive to docetaxel and are also highly cross-resistant to vinblastine. However, cross-resistance to other agents is either moderate (doxorubicin and cisplatin (resistance factor ≤3)) or absent (camptothecin or 5-FU). Although docetaxel and paclitaxel are structurally similar, docetaxel is still able to inhibit tumour cell replication of paclitaxel resistant J744.2 murine macrophage cells.

Determinants of innate resistance are likely to occur at the level of MAPs. Differences in MAPs (e.g., in murine mammary tumours, that is sensitive MA16/C, MA13/C and poorly sensitive MA44 to docetaxel *in vivo*) may account for the differences in docetaxel tumour sensitivity and intrinsic insensitivity in murine mammary tumours *in vivo*.

Cross-resistance to docetaxel has been observed in several multidrug resistant sublines. But it is not likely that cross-resistance to docetaxel is automatically observed in cell sublines that express the MDR phenotype. Furthermore, a lack of cross-resistance was noted with 5-FU in colon COLO/5FU-R and LOVO/5FU-R, and with cisplatin in ovarian 41McisR, CH1cisR, and OVCAR-3carboR.

Reversal of resistance to docetaxel has been examined in human myeloma cell lines, in which some chemosensitisers have proven to be useful.

Pharmacokinetics

Absorption

Evaluation of preclinical pharmacokinetics of docetaxel in non-tumour bearing mice and mice bearing colon adenocarcinoma 38 demonstrate that after bolus doses, the decline in docetaxel's concentration is biexponential, with the maximum plasma concentration proportional to the administered dose and there is a linear relationship between dose and area under the curve (AUC). At all tested doses, drug concentrations in tumour were higher than the inhibitory concentration in 50% (IC50) of KB (epidermoid carcinoma) and T24 (bladder carcinoma) tumour cell lines studied.

In mice bearing colon adenocarcinoma, the disposal of docetaxel was biphasic, with half-lives of 7 min and 1.2 h, respectively. Docetaxel displayed linear pharmacokinetics, peak plasma concentration and AUCp increased in proportion to the administered dose. At the optimal single i.v. dose of 37 mg/kg, the plasma total body clearance averaged 2.2 l/h/kg. The AUCp at doses of 13 -62 mg/kg ranged from 4.5 to 29.6 µg/ml.h.

After i.v. administration of a highly active 111 mg/m^2 dose, the plasma pharmacokinetics in normal B6D2F$_1$ mice and in colon adenocarcinoma 38 tumour-bearing mice were similar. Pharmacokinetic parameters of docetaxel in mice, rats and dogs after single dose and as unlabeled product are presented in Table 1.

Table 1: Pharmacokinetic Parameters of Docetaxel in Mice, Rats and Dogs (Single Dose, Unlabeled Product)

Parameters	Normal Mouse	Tumour Bearing Mouse (C38)	Rat	Dog
i.v. Dose (mg/m^2)	111	111	30	30
Co (µg/ml)	54[a]	51[a]	4.1[b]	3.5[b]
AUC0→∞ (µg.h/ml)	24.4	17.1	0.91	1.7
t1/2α(h)	0.15	0.12	0.02	0.07
t1/2β(h)	1.12	1.18	0.78	6.6
Vdss (l/kg)	1.6	2.2	4.0	9.1
Clt (l/h/kg)	1.5	2.2	5.5	0.9

[a] Extrapolated value (bolus administration)
[b] Concentration at the first sampling time, that is, 2 min post end of infusion (10 min duration)
In the rat, plasma docetaxel half-lives were comparable to those in the mouse: 0.014-0.21 h for the first phase and 0.78=1.66 h for the second phase. For doses above 15 to 60 mg/m^2, AUC increased proportionally from 0.6 to 2.5 µg.h/ml. However, at 120 mg/m^2 the increase was more than proportional (9.4 µg.h/ml).
In mice, docetaxel showed a good proportionality of plasma Cmax, plasma AUC and tumour AUC values with i.v. administered doses of 39 to 186 mg/m^2.

In order to support the claim that the differences in formulation of the proposed and reference products do not impact on the behaviour of the product the Applicant submitted an *in vivo* comparative plasma concentration study of Docefrez versus Taxotere in male Spague Dawley rats. The results suggest that the docetaxel concentration levels in plasma after administration of Docefrez and Taxotere were comparable and the differences in the drug concentrations were not statistically significant. The comparable plasma levels indicate that drug release from micelles is similar from Docefrez and Taxotere.

Distribution

Kinetic studies of radiolabelled docetaxel disposal in mice demonstrated that it is rapidly distributed with an apparent distribution half-life of 10 min. Plasma protein binding ranged from 76 to 89%. Tissue uptake of radiolabelled docetaxel is rapid, especially in the liver, bile, intestine and gastric contents, as well as in haematopoietic tissues, muscle, the salivary glands and pancreas. But docetaxel was not found in the CNS.

The highest mean tissue concentrations of docetaxel after i.v. administration are observed in the heart and the liver (26.1 ± 7.8 and 25.3 ± 26.1) as compared to that after i.p. administration in the abdominal wall and colon (23.6 ± 15.1 and 21.7 ± 5.7), respectively. These differences post i.v. and i.p. administration are statistically significant in the heart (p=0.0079), stomach (p=0.0159), colon (p=0.0159) and abdominal wall (p=0.0079).

At all doses, tumour docetaxel levels were considerably higher than the IC50 values of cytotoxicity in tumour cell cultures, up to 24 h after administration. This long exposure of tumour tissue may be an essential factor for docetaxel activity in human patients, where plasma exposure at therapeutic doses is in the same range as in the mouse (4.7 µg.h/ml at 100 mg/m^2).

In vivo plasma protein binding of the radiolabelled compound was high in mice and rats (from 84.1 to 89.1% at 0.25 h). Binding to plasma proteins *in vitro* was also high in mouse (8995 %), rat (70-76%), dog (83-89%) and man (79-83%). Among human plasma proteins, it was mainly bound to albumin and α1-acid glycoprotein (AAG), the association with the latter might be concentration dependent.
Docetaxel is found to be active i.p and i.v. against s.c. implanted tumours, indicating that it crosses physiological barriers well. But it is inactive by the p.o. route, probably as a result of de-esterification and cleavage of the molecule at the acidic pH of the stomach.

Metabolism

Hepatic metabolism and biliary excretion is the major pathway of docetaxel elimination in all species. Only a minor fraction of the dose is excreted in the form of parent drug.

In the mouse, docetaxel is almost completely metabolised. Only a minor fraction (<20%) of the parent drug is eliminated unchanged in the mouse, dog and rat excreta, rat bile and human faeces.

Docetaxel is primarily metabolised by successive oxidation of the tert-butyl ester group on the side chain, with cyclisation occurring for the aldehyde and acid derivatives with the resultant alcohol derivative being the most abundant metabolite. A minor pathway is caused by 7epimerisation.

In vivo metabolism studies in the mouse, the rat, the rabbit and the dog did not indicate any major species or gender differences in the metabolic pathway. The main enzymes involved in docetaxel metabolism are monooxygenases (phase I enzymes). Studies in rat liver microsomes and in the isolated perfused rat liver also indicated a major role of CYP3A in this species. Metabolism of docetaxel was also found to be similar in rat, pig, minipig and human liver microsomes and cDNA-expressed P450 enzymes leading to similar products of metabolism through CYP3A orthologs. Docetaxel is oxidised to metabolites that are less antineoplastic than the parent drug and the antineoplastic effects of taxanes observed *in vivo* were concluded to be apparently related to metabolic rates rather than metabolic profiles.

Excretion

Following rapid tissue uptake (especially in liver and kidneys), the elimination of docetaxel in normal tissues is biphasic with terminal half-lives ranging from 2.2 to 4.5 h. However the elimination half-live of docetaxel from tumour sites is approximately 22 h, suggesting long tumour site retention and thus very slow elimination. At a dose of 37 mg/kg, AUCt, and plasma AUC in the tumour values were 84 µg/g.h and 17 µg/ml.h, respectively. For a 111 mg/m^2 dose, elimination

half-life tumour levels of docetaxel were noted to be 1.29 µg/g even 24 hrs after administration. This high affinity of docetaxel for tumour tissue *in vivo* is consistent with that for tumour cells *in vitro* and the observation of a slow efflux.

Studies of radiolabelled docetaxel in mice and dogs showed the drug's elimination to be primarily biliary and hepatic, while urinary excretion was less than 10% and pulmonary excretion was negligible. Biliary excretion accounted for 75% of the dose, in three major metabolites. Radioactivity was detected in all tissues except the CNS. Several metabolites, each representing less than 2% of the administered dose were recovered in the urine.

Toxicology

Preclinical general toxicology studies of docetaxel have been carried out in Beagle dogs, CD2F1 mice and rats.

Single dose toxicity

Single i.v. dose studies (X1) or once daily i.v. dosing of docetaxel for 5 days (X5) demonstrated dog to be the most sensitive species to the toxic effects of docetaxel. In single dose studies, docetaxel principally affected tissues with a high cell turnover such as the gastrointestinal epithelium (dog), haematopoietic and lymphatic organs (all species), and testis (rodents). Hemopoietic toxicity, including leucopenia, thrombocytopenia, bone marrow aplasia, and involution of the lymphoid organs, was consistently observed in all three species. The dose limiting toxicities were digestive tract lesions, and myelosuppression associated with peripheral leucopenia. Hypotension was also observed in the dog but this was attributed to polysorbate 80. When single dose (X1) and X5 schedules were compared, similar cumulative haematopoietic toxicity was observed with the 5 day schedule.
Neurotoxicity was present in mice only, and testicular toxicity occurred in both mice and rats. In dogs, gastrointestinal effects were the dose-limiting toxicity. In dogs, single doses of 70 or 50 mg/m^2 were severely toxic and/or lethal. In rats, mortality occurred following single doses of 120 mg/m^2 of docetaxel and above. A single dose of 60 mg/m^2 was the 'highest non-lethal dose' (HNLD). The single-dose LD50 in mice was 414 mg/m^2 and the HNLD was 285 mg/m^2. Haematopoietic toxicity was cumulative in both mice and dogs, as were testicular and neuromotor changes in mice and lethal digestive toxicity in dogs. Haematopoietic toxicity was reversible, neurotoxicity was partially reversible and testicular effects were not reversible within the 28 day recovery period following treatment. Animal toxicology failed to show evidence of fluid retention or increased capillary permeability.

Repeat-dose toxicity

Multiple-dose toxicity studies in rats, dogs, and monkeys, given docetaxel at 21-day intervals for 10, 10, and 12 courses, respectively, showed no evidence of increased incidence or severity of adverse effects with successive treatment courses. No local irritation was observed at the injection site during single, 5-day, and intermittent-dose animal studies. The intravenous formulation of docetaxel does not possess significant sensitisation or vesicular potential.

Five-day cumulative toxicity studies in mice and dogs indicated that the incidence and severity of adverse effects at cumulative dose levels were comparable to those at corresponding single-dose levels. The cumulative 5-day LD50 in mice was 450 mg/m^2, which correlates with the single dose LD50 of 414 mg/m^2. In dogs, GI toxicity and leucopenia of cumulative daily doses were of severity corresponding to comparable single-dose levels: five daily doses of 6 mg/m^2 produced adverse effects comparable to those following a single dose of 30 mg/m^2. Administration as an intermittent-dose regimen should allow for resolution of hemopoietic adverse effects and minimise cumulative toxicity. Furthermore results of intermittent-dose studies demonstrated that docetaxel may be administered for up to 12 treatment courses without increasing the severity of principal (particularly haematopoietic) toxicities.

Genotoxicity

In mutagenicity tests, docetaxel was found to have no effect on five strains of *Salmonella typhimurium* or on one strain of *Escherichia coli*. Genotoxicity tests indicated that docetaxel was non-mutagenic and non-clastogenic. However, *in vitro* and *in vivo*, docetaxel has produced an increase in the number of micronucleated, aneuploid and polyploidy cells, which can be interpreted

a mutagenic potential. Docetaxel has been shown to be mutagenic in the *in vitro* micronucleus and chromosome aberration test in CHO-K1 cells and in the *in vivo* micronucleus test in the mouse. It did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assay.

Carcinogenicity

No studies have been submitted.

Reproductive and developmental toxicity

Foetal toxicity was observed in rats administered maternally toxic doses of docetaxel. A significant reduction in the number of corpora lutea and implantations, litter size and number of live births was reported. Treatment of pregnant rats and rabbits with daily doses up to 1.8 mg/m^2 and 2.4 mg/m^2, respectively, during the organogenesis phase of gestation demonstrated that docetaxel increases post-implantation loss, reduces fetal weight, and delays fetal ossification. In rabbits, 2.4 mg/m^2/day was lethal to most of the dams and a dose of 1.2 mg/m^2 produced marked maternal toxicity. External, skeletal or visceral malformations were not reported, suggesting that docetaxel was embryo- and fetotoxic but not teratogenic.

Adverse effects on the testis observed in rodent toxicity studies suggest that docetaxel may impair male fertility.

Studies on impurities

The Applicant has submitted an *in vivo* study in mice to compare the acute toxicity after a single i.v. dose of Docetaxel for injection with 1% 7-epimer impurity, the vehicle control and Taxotere. A total of 20 male and 20 female mice per group were dosed at 40 or 80mg/kg. The route of administration was i.v. which is the proposed clinical route. Doses were selected on the basis of the reported human MTD at 115mg/m^2 which when converted to the dose in mice is 38.13 mg/kg. Therefore one dose was selected at 40mg/kg (approximately equivalent to human MTD) and the other at 80 mg/kg (double the equivalent of human MTD) for both Docefrez and Taxotere.

There were no deaths in animals treated with either Docefrez with 1% 7-Epimer impurity or Taxotere. Histopathologically, there were no major differences in microscopic findings between Docefrez and Taxotere. This indicates that under the conditions of the study, the acute toxicity of Docefrez with 1% 7-Epimer impurity is comparable to that of Taxotere.

Guideline ICH Q3B states that in order to qualify above the applicable threshold of 0.2% of this impurity, two types of genotoxicity studies are required in addition to a toxicity test: (i) point mutation (ii) chromosomal aberration. The Applicant has conducted only the former: the submitted AMES test. However, the Applicant has agreed to reduce the release and end of shelf-life limit for 7-epi-docetaxel from initially NMT 1% to NMT 0.3% which is in line with the docetaxel active substance monograph in the Ph Eur. The CHMP considered this to be acceptable.

Local tolerance

Local tolerance and sensitisation studies results suggest a good tolerance and absence of a significant sensitisation potential of the i.v. formulations of docetaxel.

Ecotoxicity/environmental risk assessment

An ERA has not been submitted.

Discussion on Non-Clinical aspects

The clinical efficacy and safety of docetaxel containing products has been well established in a comprehensive literature review. In addition, in order to support the claim that the differences in formulation of the proposed and reference products do not impact on the behaviour of the product the Applicant has submitted three non-clinical studies that have supported the claim of equivalence of Docefrez to the reference product.

Guideline ICH Q3B states that in order to qualify above the applicable threshold of 0.2% of this impurity, two types of genotoxicity studies are required in addition to a toxicity test: (i) point mutation (ii) chromosomal aberration. The Applicant has conducted only the former: the submitted AMES test.

The qualification limits set for the impurity 7-epimer are higher than the qualification threshold of 0.2% mentioned in the ICH Q3B(R2) for new drug products. However, the Applicant has agreed to reduce the release and end of shelf-life limit for 7-epi-docetaxel from initially NMT 1% to NMT 0.3% which is in line with the docetaxel active substance monograph in the Ph Eur. The CHMP considered this to be acceptable.

According with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), the lack of ERA studies is acceptable.

2.4 Clinical Aspects

Introduction

The Applicant has provided an updated review of the clinical use of docetaxel for the proposed indications with 34 publications from 1994 to 2008.

There were no detailed study reports from clinical trials submitted by the Applicant. The application was submitted in accordance with Article 10(3) of Directive 2001/83/EC, where the Applicant was not required to provide the results of pre-clinical tests and of clinical trials as the medicinal product is a generic (hybrid) of a reference medicinal product which is authorised for 6/10 years in a MS or in the Community.

Exemption

The Applicant has claimed that Docefrez, a lyophilised powder to be reconstituted with solvent, has after dilution in the recommended infusion fluid, the same drug concentration of docetaxel as the reference product Taxotere. Docefrez according to the Applicant contains the same active substance with a similar composition and pharmaceutical form at the time of administration and is recommended for administration through the same route, that is, intravenous, as Taxotere. The Applicant has claimed that according to the CPMP guideline "Note for Guidance on the Investigation of Bioavailability and Bioequivalence" (CPMP/EWP/QWP/1401/98), there is no requirement for a bioequivalence study for such products.

The CHMP was of the opinion that Docefrez, like the reference product Taxotere, is a micellar solution, and in this regard it may be considered as 'complex'. Therefore comparable data regarding the main characteristics of the micellar solution (physico-chemical properties, micelle size and size distribution) were required (see Quality section). The results of these studies confirmed pharmaceutical comparability of Docefrez and the reference product Taxotere and therefore bioequivalence studies were not required.

Clinical studies

The application contains adequate clinical data from the review of the publication literature submitted for the proposed indications:

Breast cancer

Docefrez in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

Docefrez 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.

Docefrez 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.

Docefrez in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 and who previously have not received chemotherapy for metastatic disease.

Docefrez 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

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

Docefrez 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

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

Gastric adenocarcinoma

Docefrez 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

Docefrez 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.

In the adjuvant treatment of operable node-positive breast cancer, the recommended dose of docetaxel is 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles. For the treatment of patients with locally advanced or metastatic breast cancer, the recommended dose of docetaxel is 100 mg/m^2 in monotherapy. In first-line treatment, docetaxel 75 mg/m^2 is given in combination therapy with doxorubicin (50 mg/m^2). In combination with trastuzumab the recommended dose of docetaxel is 100 mg/m^2 every three weeks, with trastuzumab administered weekly. In combination with capecitabine, the recommended dose of docetaxel is 75 mg/m^2 every three weeks, combined with capecitabine at 1250 mg/m^2 twice daily (within 30 minutes after a meal) for 2 weeks followed by 1-week rest period.

In chemotherapy naïve patients treated for non-small cell lung cancer, the recommended dose regimen is docetaxel 75 mg/m^2 immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes. For treatment after failure of prior platinum-based chemotherapy, the recommended dose is 75 mg/m² as a single agent.

The recommended dose of docetaxel for prostate cancer patients is 75 mg/m^2. Prednisone or prednisolone 5 mg orally twice daily is administered continuously (see section 5.1).

The recommended dose of docetaxel for gastric adenocarcinoma patients is 75 mg/m^2 as a 1 hour infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3 hour infusion (both on day 1 only), followed by 5-fluorouracil 750 mg /m^2 per day given as a 24-hour continuous infusion for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks.

For the induction treatment of inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel is 75 mg/m^2 as a 1 hour infusion followed by cisplatin 75 mg/m^2 over 1 hour, on day one, followed by 5-fluorouracil as a continuous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. For the induction treatment of patients with locally advanced (technically unresectable, low probability of surgical cure, and aiming at organ preservation) squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel is 75 mg/m^2 as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3 hour infusion, followed by 5-fluorouracil 1000 mg/m^2/day as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles.

Pharmacokinetics

The pharmacokinetics of docetaxel has been shown to be linear, with first order elimination. In dose ranging studies, AUC increased in proportion to dose and total plasma clearance was independent of dose. Following the administration of a 100 mg/m^2 dose, given as a 1 h infusion, a mean peak plasma level of 3.7 µg/ml was obtained; with a corresponding AUC of 4.6 h.µg/ml. Mean values for total body clearance and steady-state volume of distribution were 21 l/h/m^2 and 113 l. Inter-individual variation in total body clearance has been shown to be approximately 50%. Total clearance was 27% lower on average in patients with mild to moderate liver function impairment. Docetaxel clearance was not modified in patients with mild to moderate fluid retention and docetaxel pharmacology is unlikely to be altered in patients with kidney impairment, as renal excretion is responsible for <5% docetaxel elimination. Docetaxel is extensively bound (>95%) to plasma proteins both *in vivo* and *in vitro*, predominantly to α1-acid glycoproteins, albumin and lipoproteins. Docetaxel is metabolised via hepatic cytochrome P450 isoenzyme CYP3A4 and excreted chiefly in the faeces as metabolites. A study of ^{14}C-docetaxel showed that approximately 80% of the radioactivity recovered in faeces is excreted during the first 48 hrs as one major inactive metabolite and 3 minor inactive metabolites and very low amounts of unchanged drug.

Pharmacodynamics

Docetaxel has been shown *in vitro* to disrupt the microtubular network in cells, which is essential for mitotic and interphase cellular functions. Docetaxel acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin.

Additional data

No additional studies were submitted.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule should follow the PSUR schedule for the reference product.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the legislative requirements.
The MAH must ensure that the system of pharmacovigilance, as described in version 6 (dated January 2010) presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

- **Risk Management Plan**

Not applicable. The application is based on a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified.

- **User consultation**

The user testing of the package leaflet was performed. The criterion for a successful Readability Test was fulfilled. The user testing of the package leaflet was judged acceptable.

Discussion on Clinical aspects

Docefrez meets the requirement on safety and efficacy required for a marketing authorisation application under Article 10 (3) 'hybrid application' and a biowaiver for not submitting bioequivalence studies has been granted. Therefore no further clinical data was required. The

current knowledge concerning the safety and efficacy of docetaxel has been evaluated by means of an updated literature search.

A RMP was considered not required as the application concerns a medicinal product containing a known active substance for which no additional safety concerns requiring specific risk minimisation activities have been identified with respect to the reference medicinal product. The active substance has been in use for many years and the safety profile of the products is well established. It was considered that routine pharmacovigilance according to the Detailed Description of Pharmacovigilance System was sufficient for safety monitoring.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality, non clinical and clinical data. 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.

Recommendation

”Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Docefrez in the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, head and neck cancer was favourable and therefore recommended the granting of the marketing authorisation.