The gastrointestinal and hematopoietic effects were reversible, whereas testicular and neurotoxic effects were partially reversible or irreversible. Overall, these effects are consistent with the toxicities observed with other antimitotic agents.

Repeated-dose toxicity

- *Five-day repeated dose toxicity*

Table 4 summarises the results obtained in 5-day repeated toxicity studies in mice and dogs.

Table 4. Results of 5-day sub-acute studies in mice and dogs (dogs in mg/m^2)

	Dog		Mouse	
	Daily dose	*Cumulative dose*	*Daily dose*	*Cumulative dose*
HNTD	3	15	6	30
HNLD	6	30	30	150
LD_{10}	NA	NA	60	300
LD_{50}	NA	NA	90	450
LD	15	75	136	680

Docetaxel administered as a daily regimen showed a cumulative toxicity. Docetaxel should therefore preferably be given as an intermittent-dose regimen to allow recovery of haematopoietic effects.

- *Intermittent-dose toxicity studies*

Docetaxel was administered at 21 days intervals. Up to 10 (rat and beagle dog) and 12 (cynomolgus monkey) subsequent courses were given.

Studies in rats at doses up to 60 mg/m^2 for 3 or 10 treatment courses, showed hematopoietic toxicity, thymic and testicular atrophy. Studies in dogs at doses up to 30 mg/m^2 for 5 or 10 treatment courses, showed hematopoietic and gastrointestinal toxicity and dermal effects (similar as the observed at single-dose and repeated dose studies).

Studies were performed in monkeys at doses of 25 mg/m^2 and 50 mg/m^2, however the highest dose was discontinued due to the severity of the toxicity. Toxic effects found at 25 mg/m^2 after 12 treatment courses were: moderate neutropenia/ lymphopenia, mild reduction in RBC parameters and moderate gastrointestinal toxicity.

In all species haematological parameters recovered during day 21 of the period in between treatment courses. In addition, no increase of severity or incidence of adverse effects was seen with the progression of the study.

Local tolerance and sensitization

Tolerance studies in rabbits at doses 3 times higher than administered to humans, including i.v., intradermal or intra-arterial routes, have shown good tolerance. External and histopathological evaluation of injection sites in toxicity studies revealed no signs of irritation.

In mice, guinea pigs and rabbits there was no evidence of sensitisation. However, a mild reaction was seen following intradermal re-challenge of docetaxel in pre-treated rabbits.

Genotoxicity

Docetaxel has been evaluated for potential genetic toxicity in a battery of standard tests *in vitro* and *in vivo*. Results of genotoxicity have indicated that docetaxel is neither mutagenic nor clastogenic, however it increased the incidence of micronucleated, aneuploid and polyploidy cells *in vitro* and *in*

vivo. This effect is consistent with the pharmacological activity of the drug on microtubules and has been reported for other antineoplastic drugs.

Carcinogenicity

No carcinogenicity studies have been submitted.

Reproductive toxicity

Fertility studies in male and female rats have shown that docetaxel produced maternal and paternal toxicity with a reduction in fertility parameters. It was considered to be embryotoxic at daily doses > 0.9 mg/m^2.

Docetaxel was also studied in pregnant rats and rabbits treated during the organogenesis phase of gestation. It was shown that docetaxel was embryotoxic and foetotoxic, however it was not teratogenic.

Studies on impurities
The impurities specified in Doctaxel Teva, concentrate and solvent for solution for infusion are:

- Two specified impurities, both present at a concentration in accordance with ICH Q3B(R2) requirements and within qualification threshold of 0.2%.

- 10-Oxodocetaxel for which the accepted qualification limit is 0.4 % at release. The Applicant has provided a description of toxicological aspects and a toxicity prediction assessment for this impurity. The influence of the chemical group on the 10-position of the main ring structure of taxanes has been well characterized. Compounds related to taxol or docetaxel and modified on the 10-position have been tested for antitumour activity by several different research groups. All authors of the cited references conclude that the chemical group at the 10-position is not essential for the cytotoxicity of taxanes. Branching of large groups on the 10-position results in a loss of activity, but compounds without a functional group or with any polar substituent are as potent as taxol. Although this has mainly been investigated for taxol-derivates, results on 10-deoxytaxotere demonstrated that also for docetaxel the group on the 10-position makes only a small contribution to the antitumor activity. No antitumour activity has been measured for the impurity 10-oxo-docetaxel itself, neither has a toxicological study been done. However, based on the antitumour activity of 10C-derivatives, the pharmacological activity of 10-oxo-docetaxel is considered to be in line with other 10C-derivatives and thus comparable to that of docetaxel itself. No accumulation of 10-oxo-docetaxel will occur in the body, as 10-oxo-docetaxel will be metabolized in the same way as docetaxel itself, which is mainly on the side chain.

  In addition toxicity prediction assessment was carried out using the DEREK database to assess the potential toxicology of 10-oxo-docetaxel. The analysis revealed three structural alerts including nephropathy in rodents and considered not to be a hazard to human health. Also, a potential to cause skin sensitisation but of minor concern taking into account the intravenous route of administration and a third structural alert. This third alert refers to chromosome damage in vitro in human cells that is predicted plausible for 10-oxo-docetaxel. In conclusion, the pharmacological/toxicological profile of 10-oxo-docetaxel does not differ from that of the parent compound.

Environmental Risk Assessment

No environmental risk assessment has been submitted.

Discussion on Non-Clinical aspects

The non-clinical literature review presented by the Applicant provided an adequate overview of the pharmacological, pharmacokinetic and toxicological aspects of docetaxel. There were no major issues raised for the approval of Docetaxel Teva, concentrate and solvent for solution for infusion.

The qualification limits set for the impurity 10-Oxodocetaxel are higher than the qualification threshold of 0.2% mentioned in the ICH Q3B(R2) for new drug products. However 10-Oxodocetaxel is not a novel impurity, being allowed up to 0.3% in the draft PhEur specification for docetaxel trihydrate drug substance. Since drug product specifications are generally more relaxed than those for drug substances, a release level of 0.4% for the 10-oxodocetaxel impurity in drug product is considered reasonable. Qualification limits on impurities might be exceeded on a case by case basis if properly justified as it has been the case for Docetaxel Teva, a semi-synthetic drug substance from plant origin. DEREK and SAR assessments did not reveal any toxicology profile different from the parent compound. In addition, taking into account that docetaxel is intended to treat advanced stage cancer patients and it is not intended as a long-term treatment, additional studies are not warranted since it is not likely to have an impact on the clinical efficacy or safety of the product and its predicted side effects are already covered in the labelling for originator product. Taking into account all these considerations, specification limits of 0.4 at release are acceptable for the impurity 10-Oxodocetaxel.

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 95 publications from 1993 to 2008.

There were no detailed study reports from clinical trials submitted by the applicant. The application was submitted in accordance with Article 10(1) 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 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 Docetaxel Teva, concentrate for solution for infusion, is an aqueous intravenous solution containing the same active substance in the same concentration as the reference product, and therefore, it is subject to the exemption of bioequivalence studies (as per Section 5.1.6 of the guideline "Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98").

Docetaxel Teva , like the reference product Taxotere, is a micellar solution, and in this regard it may be considered as 'complex'. Therefore data about the main characteristics of the micellar solution (physico-chemical properties, micelle size and size distribution) in the product ready to use as well as comparison data with the micellar solution from Taxotere were submitted (see Quality section). Results of these studies confirmed pharmaceutical comparability of Docetaxel Teva and the reference product Taxotere, thus 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

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

Docetaxel Teva in combination with doxorubicin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.

Docetaxel Teva monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent.

Docetaxel Teva 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.

Docetaxel Teva in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.

Non-small cell lung cancer

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

Docetaxel Teva in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition.

Prostate cancer

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

Gastric adenocarcinoma

Docetaxel Teva in combination with cisplatin and 5-fluorouracil is indicated for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease.

Head and neck cancer

Docetaxel Teva 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, determined in 23 patients receiving 20-115 mg/m^2, are linear, with clearance independent of the administered dose and with plasma AUC increasing in proportion to dose.

The pharmacokinetic profile of docetaxel is consistent with a three-compartment model at clinically relevant doses (60-100 mg/m2). Half-lives for the α, β and γ were 4 minutes, 36 minutes and 11.2 hours, respectively after a dose of 100 mg/m^2 after 1 hour infusion. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Following the administration of a 100 mg/m^2 dose given as a one to two hour infusion a mean peak plasma level of 2.41-3.67 μg/ml was obtained with a corresponding AUC of 4.59-5.93 μg.h/ml. Mean values for steady-state volume of distribution were 67.3-149 1/m^2. In vitro studies have demonstrated that docetaxel is extensively bound to albumin and α-acid glycoprotein and that the latter is the main determinant of variability in docetaxel serum binding. In human plasma docetaxel was found to be bound for more than 98%. It is not known whether docetaxel is distributed into breast milk.

Docetaxel is primary metabolized by the cytochrome P450 (CYP) 3A4 isoenzyme to one major and three minor largely inactive metabolites (RPR104952 (hydroxydocetaxel) and for subsequent oxidation of RPR104952 to RPR111059 and RPR111026). The major pathway of elimination of docetaxel is hepatic metabolism. Docetaxel metabolites are produced by successive oxidation (to alcohol, aldehyde and then acid) of the tert-buty ester group on the side-chain. Based on catalytic potential, CYP3A4 and CYP3A5 are the most important enzymes among the four members of the CYP3A subfamily (CYP3A4, CYP3A5, CYP3A7, CYP3A43) involved in docetaxel metabolism and elimination. The metabolites demonstrate substantially reduced cytotoxic activity compared with the parent drug, making biotransformation by CYP3A a major route of inactivation. A few small studies demonstrated that variation in CYP3A activity, as assessed by different probe drugs, is a determinant of docetaxel clearance. However, so far the clinical usefulness of individualized dose based on CYP3A activity has not been demonstrated by reducing inter-individual variability in docetaxel pharmacokinetics, toxicities or activity. Because of the important role of CYP3A in the metabolism of docetaxel, pharmacokinetic interactions with drugs that influence the activity of these enzymes or that are metabolized by the enzymes are to be expected. The major metabolites of docetaxel and < 10% of the parent drug are excreted primarily in the faeces via the biliary tract, with only a small proportion (<10%) excreted unchanged in the urine. In a study in three patients with cancer, faecal and urinary excretion accounted for ~75% and 6% of a radiolabelled dose of docetaxel within 7 days. The majority of the dose recovered in the faeces was excreted in the first 48 hours (~ 80% as metabolites and <8% as unchanged drug). In addition to CYP3A-mediated elimination, docetaxel is also a substrate for the efflux membrane-localised transporter P-glycoprotein, encoded by the gene ABCB1. ABCB1-mediated intestinal secretion has been demonstrated to contribute significantly to faecal elimination of taxane drugs both in mice lacking ABCB1 and in humans.

Renal excretion of unchanged docetaxel is very low (<5% of the dose). The major pathway of elimination of docetaxel is hepatic metabolism followed by biliary excretion. Mean values for total body clearance was 21 l/h m^2. The pharmacokinetic profile of docetaxel is characterized by substantial interpatient variability. In a population pharmacokinetic study of more than 600 patients receiving docetaxel 75-100 mg/m^2, which used a limited sampling scheme with the last sampling time-point at 24 hours post-infusion, the median clearance was 36 l/h (5th-95th percentile: 17-59 l/h), representing approximately 3.5-fold variation in this population. In a more recent study in which patients received docetaxel 75 mg/m^2 and an extended sampling scheme to 8 days post infusion was utilized, approximately 10-fold variation in drug clearance was observed when patients with outlier values were not excluded from the analysis.

Pharmacodynamics

No studies have been submitted.

Additional data

No additional data has been 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 for Docetaxel Teva should follow the PSUR submission scheduled for the reference medicinal product, Taxotere.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system, version 6 dated 21 Nov 2008, as described by the applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market.

- **Risk Management Plan**

No description of the Risk Management Plan has to be provided by the Applicant.

Discussion on Clinical aspects

Docetaxel Teva meets the requirement on safety and efficacy required for a marketing authorisation application under Article 10 (1) 'generic' 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.

An 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 Docetaxel Teva 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.