European Medicines Agency
Evaluation of Medicines for Human Use

ASSESSMENT REPORT
FOR

Docetaxel Teva

International Nonproprietary Name:
Docetaxel

Procedure No. EMEA/H/C/1107

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@ema.europa.eu http://www.ema.europa.eu

TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Teva Pharma B.V. submitted on 04 December 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Docetaxel TEVA , in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC.

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, 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., France
- Date of authorisation: 27 November 1995
- Marketing authorisation granted by: Community
- (Community) Marketing authorisation number: EU/1/95/002/001

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Not applicable

The Rapporteur, appointed by the CHMP was Gonzalo Calvo Rojas.

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 04 December 2008.
- The procedure started on 24 December 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 March 2009.
- During the meeting on 20-23 April 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 23 April 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 August 2009.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 11 September 2009.
- During the CHMP meeting on 21-23 September 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing.
- During the meeting on 16-19 November 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for Docetaxel TEVA on 19 November 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Docetaxel Teva concentrate and solvent for solution for infusion is a generic medicinal product containing the active substance docetaxel. The reference medicinal product is Taxotere concentrate and solvent for solution for infusion authorised 27 November 1995.

Docetaxel in an antineoplastic agent that acts by promoting the assembly of tubulin into stable microtubulues and inhibits their assembly, which leads to a decrease of free tubulin and to cancer death.

The safety and efficacy profile of docetaxel for the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer has been demonstrated in several clinical trials, details of which can be found in the EPAR for the reference medicinal product. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this active substance.

The indication for Docetaxel Teva is identical to that approved for Taxotere and is as follows:

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.

2.2 Quality aspects

Introduction

Docetaxel 40 mg/ml, concentrate for solution for infusion is a clear viscous yellow to yellow-brown solution. It is supplied with an additional vial of solvent (13% ethanol in water for injection). The solvent is used to premix the concentrate in order to obtain a sterile, preservative-free solution intended for dilution with 5% glucose or 0.9% sodium chloride prior to intravenous infusion.

The excipients used in the formulation are polysorbate 80, ethanol and citric acid.

The formulation of this product is qualitatively similar to the reference product Taxotere. There are only minor quantitative differences in the amount of citric acid.

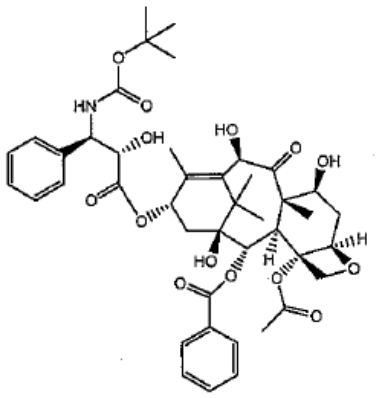
Active Substance

Docetaxel is an efficient inhibitor of eukaryotic cell replication, blocking cells in the late G2-M phase of the cell cycle. It promotes abnormal assembly of microtubules via stabilization.

Docetaxel is manufactured by two different manufacturers. The Active Substance Master File (ASMF) procedure was followed for the active substance for both manufacturers.

It is a white to off-white powder, synthesised in the anhydrous form. At 25ºC docetaxel is freely soluble in ethanol and tetrahydrofuran; sparingly soluble in acetonitrile; soluble in methanol, acetone and ethyl acetate; insoluble in n-hexane and water. Its partition coefficient (log P) is 4.26.

Docetaxel is manufactured from N-Deboc Docetaxel, which is obtained from 10- deacetyl baccatin III, a natural product extracted from yew tree. The stereogenic centres naturally occurring in 10-DAB III are kept through the synthetic processes. Docetaxel is chemically designated as N-Debenzoyl-N-(tert-butoxycarbonyl)-10-deacetyltaxol, the molecular formula is $C_{43}H_{53}NO_{14}$ and its molecular weight is 807.88.



docetaxel

- **Manufacture**

Docetaxel is manufactured in 5 steps but only one step involves chemical reactions, all other steps involve crystallisation and purification of the active substance. The route of synthesis was briefly

described in the open part but the details were provided in the restricted part of the ASMF. The process was acceptably described for both manufacturing sites.

The chemical structure was determined by XRD, IR, ^{1}H-NMR, ^{13}C-NMR, DSC and TGA and is well established. Structural studies to demonstrate the evidence of the chemical structure of docetaxel and to evaluate polymorphism, potential isomerism and solvated forms were performed. XRD results confirm that the same crystalline form is consistently obtained in the manufacturing process

Discussion about impurities and residual solvents has been presented. Impurities are well controlled in the active substance and limits are in line with ICH Q3Aand ICH Q3C guidelines.

- **Specification**

Specification is in agreement with the new monograph for docetaxel trihydrate, with relevant modifications regarding the anhydrous state.

The specification includes tests for appearance (visual examination), identification (IR, HPLC), assay, purity and related substances (HPLC), residual acetic acid (HPLC), water content (Karl Fisher), residue on ignition, heavy metals, specific rotation, residual solvents (GC) and microbial purity.

The analytical methods are essentially the same in both manufacturing sites and are suitable to control the quality of the active substance. The methods have been well described and validated according to ICH Q2 (R1).

All batches reported for both manufacturing sites comply with the specification.

- **Stability**

Docetaxel is stored in a glass flask as primary container under nitrogen atmosphere, inside a double polyethylene bag sealed individually with an appropriate tie, inside an aluminium bag. Stability studies have shown that these materials provide adequate protection for the active substance.

Stability data were performed on 6 batches stored at 40 ± 2^{o} C / 75 ± 5 % RH (accelerated conditions) for 6 months and 9 batches stored at 25 ±2^{o} C / 60 ± 5 % RH (long term conditions) for up to 36 months. Photostability studies have not been performed since it has been established that docetaxel is unstable when exposed to UV light in solution and in solid form.

The parameters tested included appearance, assay, purity and water content. The results provided did not show significant degradation and the batch data are in compliance with the proposed specification. An agreed re-test period has been established.

Medicinal Product

Docetaxel Teva 40 mg/ml concentrate for solution for infusion is a clear viscous yellow to yellow-brown solution available in 0.5 ml and 2 ml single use vials. It is supplied with an additional vial of solvent (13% ethanol in water for injection). The solvent is a clear colourless solution, available in vials containing 1.5 ml and 6 ml of the solvent solution. The solvent is used to premix the concentrate in order to obtain a sterile, preservative-free solution intended for dilution with 5% glucose or 0.9% sodium chloride solution prior to intravenous infusion.

The container closure system for both the concentrate and the solvent consists of clear glass Type I vials closed with a bromobutyl stopper capped with aluminium seal with a propylene cover.

- **Pharmaceutical development**

The formulation of Docetaxel is qualitatively similar to that of the reference product Taxotere 40 mg/ml concentrate, manufactured by the innovator company Sanofi Aventis. The excipients used in the formulation are polysorbate 80 and citric acid. Polysorbate 80 is used as a solubiliser and citric acid as an acidifying agent. The active substance is insoluble in water and solubilisation is achieved by adding a surfactant to the formulation. Polysorbate 80 forms drug micelles and precipitation of the drug in aqueous solution does not occur. Citric acid is used in the formulation for chemical stability of the active substance. All the excipients comply with their respective European Pharmacepoeia monograph. Satisfactory certificates of analysis have been provided for all excipients.

It was considered that small differences in citric acid content between generic and reference product would be unlikely to have any significant effect on micelle characterisation or disposition of docetaxel *in vivo*.

Although the composition of Docetaxel Teva and Taxotere differ only in the amount of citric acid present, but considering the micellar nature of the product, it was important to characterise the micelle solution and compare it to the reference product prior to administration, i.e., in the infusion bag. The characterisation of the micelle solution included the determination of the pH, micelle size and micelle size distribution. The results of the studies showed the similarity of both products with regards to micellar characteristics. Considering these comparable *in vitro* results and the similarity of this generic formulation to the formulation of the reference product, it was considered that taken together, these findings could be used to support a biowaiver for this 'complex' injectable.

- **Adventitious Agents**

None of the excipients used in the formulation of docetaxel concentrate for solution for infusion are of animal origin.

- **Manufacture**

The manufacturing process for Docetaxel Teva comprises four main steps (using a non-standard process): preparation of the bulk solution, sterile filtration (0.2 μm), aseptic filling, followed by closing the vials and packaging. Prior to preparation of the bulk solution polysorbate 80 is purified.

Batch analysis data on three production scale batches confirmed that the defined process reliably produces product which meets the proposed release specification.

The solvent for docetaxel 40 mg/ml concentrate for solution for infusion is manufactured using a standard process comprising sterile filtration and final sterilization. The process is well defined and controlled. Validation data was provided on two production scale batches.

- **Product Specification**

The specifications for Docetaxel 40 mg/ml concentrate for solution for infusion include tests for: appearance (visual examination) identification (U-HPLC retention time and UV absorption), assay of docetaxel (HPLC), related substances (HPLC), colour of solution, particulate contamination (visible particles), clarity, closure integrity, extractable volume, particulate contamination (subvisible particles), pH, sterility and bacterial endotoxins. The analytical methods for assay of docetaxel and related substances were well described and validated. All other methods are described in the PhEur and therefore validation was deemed to be unnecessary.

Batch results were provided for four batches of the finished product. The results were to be in compliance with the proposed specification.

- **Stability of the Product**

Two bulk solutions of docetaxel 40 mg/ml concentrate for solution for infusion have been manufactured at the commercial site using the commercial process at production scale and filled in two batches of 0.5 ml and two batches of 2.0 ml presentation,. These four batches have been stored at 5ºC±3ºC (long term conditions) for up to 12 months and at 25ºC±2ºC/60%±5% RH (accelerated conditions) for 6 months. The results of all studies complied with the product specification in all batches and no changes were observed. Additional in-use stability data of the product diluted with 5% glucose and 0.9% sodium chloride were also provided. The in-use stability data demonstrated that the product ready to use is physically and chemically stable in the in-use conditions defined in the SPC. This was further supported by the studies performed on the characterisation of the micellar solutions.

In summary, the stability results support the shelflife and storage conditions as defined in the SPC.

Discussion on chemical, and pharmaceutical aspects

The active substance and finished product have been adequately described. The finished product is manufactured using a non-standard process. Sufficient validation data has been provided to assure that the process is robust and well controlled and produces a uniform product. The medicinal product consists of a micellar solution, i.e., the active substance is solubilised in surfactant micelles. The differences between the generic and the reference product in terms of formulation, including amount of citric acid have been shown not to affect the relevant physico-chemical properties of the product with particular regard to the characteristics of the micellar phase. Therefore, similarity between Docetaxel Teva and the reference product Taxotere can be accepted and no additional human bioequivalence study was considered necessary in this particular case.

2.3 Non-Clinical aspects

The Applicant has submitted 72 publications up to 2008. No further studies are required and the applicant has justified why no such data was provided.

Pharmacology

Docetaxel is an antineoplastic agent that belongs to the taxoid class and promotes formation of stable microtubules that are resistant to disassembly. Microtubules are components of eukaryotic cells that play a relevant role in chromosome movement during mitosis, regulation of cell morphology, hormone secretion, transport of granules, anchorage of receptors in the membrane and cellular motility. Cells exposed to taxoids accumulate dysfunctional microtubules that can not undergo the normal mitotic process and results in cell death. Docetaxel enhances both, the rate and the extent of microtubule assembly, inhibiting depolymerization.

Docetaxel acts at the level of tubulin. Tubulin is the main component of microtubules. In normal conditions, there is equilibrium between tubuline and microtubules.

In vitro studies

Docetaxel is an inhibitor of cell replication *in vitro* and it has been found to be cytotoxic against both murine and human cell lines. These cytotoxic effects are greater on proliferating rather than quiescent cells. About thirteen human cell lines from various tumour types have been exposed to increasing concentrations of docetaxel over 24 h, resulting in a plateau-shaped dose response curve. Increased cell death is therefore more dependent on exposure duration than on concentration. In several human ovarian carcinoma cell lines including lines resistant to cisplatin and carboplatin, docetaxel was 1000 times more cytotoxic than cisplatin and etoposide; and 100 times more than doxorubicin.

In vivo studies

Docetaxel activity has been studied in different tumour models including murine (Table 1) and human (Table 2) xenografts in nude mice.

Table 1. *In vivo* anti-tumour activity of docetaxel against murine tumours.

Tumour	Highest non-toxic i.v. dosage (mg/kg/dose)	Schedule days	Total dose (mg/kg)	T/C [a] (%)	T-C [b] (days)	Total log cell kill [c]	Activity rating [d]
Solid tumours s.c.							
Melanoma B 16 early	24	3.5.7.9	96	0	18.8	3.8	++++
Pancreas PO2	32.2	3.5.7	96.6	39	-	-	+/-
Pancreas PO3 early	20.5	3.5.7.9	82	0	-	6/6 cures	++++
Pancreas PO3 advanced	18.0	22.24.26.28	72	-	21.4	1.8	5/6 CR[e]
Mammary MA 16/C early	15	3.5.7	45	0	13	2.4	+++
Mammary MA 16/C advanced	10.8	7.9.11	32.4	-	14.3	2.9	5/5 CR
Mammary MA 13/C early	14.2	3.5.7	42.6	0	36	4.3	++++
Mammary MA 13/C advanced	15	24.27.30	45	-	23.9	2.5	3/5CR
Mammary MA44 early	22	3.5.7	66	39	-	-	+/-
Colon C26 early	5	1-4	20	33	-	-	+
Colon C38 early	23.5	3.5.7	70.5	0	-	7/7 cures	++++
Colon C38 advanced	26.8	14.16.18	80.4	-	16.5	1.7	5/5 CR
Colon C51 early	12.7	3.5.7	38.1	2.4	-	2.3	+++
Colon C51 advanced	15.2	10.12.14	45.6	-	17.2	1.7	++
Lewis lung early	23.2	3-7	116	5.5	6.1	1.2	+
Osteosarcoma GOS early	18.6	3-7	93	27.2	-	-	+
Hystiocytosarcoma M5076 early	8.6	3-7	43	51	-	-	-
Leukemias i.p.							
P388 10^6 cells	23.2	1-4	92.8	154	-	-	+
L1210 10^5 cells	21.7	1-4	86.8	170	-	-	++

[a] T/C % - for solid tumours: 100 x median tumour weight of the treated/median tumour weight of the controls, or for leukemias median survival time of treated animals/ median survival time for control animals.
[b] T-C in days = median time in days required for the treatment of group T and the control group C tumours to reach a predetermined size.
[c] Log cell kill = T-C in days/3.32 tumour doubling time of control mice.
[d] activity rating: ++++ = highly active (log cell kill >2.8), +++ = highly active (log cell kill = 2.0-2.8), ++ = active (log cell kill = 1.3-1.9; T/C ≥ 150% for L1210), + = active (log cell kill = 0.7-1.2; T/C= 125-174% for P388), - = inactive.
[e] CR = complete regressions

Table 2. Docetaxel evaluation against six human tumour xenografts in mice

Tumor (site)	Histology	Dose i.v. (mg/kg/injection)	Schedule (days)	Total dose (mg/kg)	T-C[a] (days)	Tumour-free survivors	Comments
CALC18 (s.c.)	Mammary adenocarcinoma	32.2	11.15.19	99	41	-	Highly active
MX-1 (s.c.)	Mammary adenocarcinoma	22	11.15.19	66	NA	10/10	Curative
LX-1 (s.c.)	Lung carcinoma	22	9.13.17	66	19.0	0/10	Active
SK-MEL-2 (s.c)	Melanoma	33	27.31.35	99	NA	10/10	Curative
OVCAR-3 (i.p)	Ovarian carcinoma	33	3.7.11	99	NA	4/10	Highly active
OVCAR-3 (i.p)	Ovarian carcinoma	33	3.10.17	99	NA	6/10	Curative
CX-1 (s.c)	Colon carcinoma	15	12.16.20	45	42.1	0/10	Active
KM20L2 (s.c.)	Colon carcinoma	33	14.18.22	99	19.3	0/10	Modest activity

[a] T/C % - for solid tumours: 100 x median tumour weight of the treated/median tumour weight of the controls

The mean optimal dose of docetaxel that produced body weight loss and no delayed toxicity was 80 mg/kg. Docetaxel has been found to be active by i.p. and i.v. routes but inactive by oral route. Different schedules of administration have been tested and it was concluded that docetaxel was schedule-independent for the maximal tolerated dose. In addition dose-response relationship has been shown.

Mechanism of resistance

The main mechanism of resistance to taxoids is due to overexpression of the cell surface drug transporter glycoprotein GP170 encoded by the multidrug resistance gene (MDR). Docetaxel has been found to be active on some but not all cell lines overexpressing the p-glycoprotein, which is encoded by the multidrug resistant gene.

Pharmacokinetics

Non-clinical pharmacokinetics of docetaxel have been investigated in mice, rats and dogs. A study in mice receiving i.v bolus doses of 13-62 mg/kg showed a biphasic plasma concentration-time curve with a short distribution half-life of 7 minutes and an apparent elimination half-life of 1h. The total body clearance was 1.6 l/h/kg and plasma AUC was 17 µgh/ml. Similar data were obtained when doses of 2.5, 10 and 33 mg/kg were administered i.v. to female FVB mice. Exposure of docetaxel in the tumours was very high (AUC range from 17 to 71 µgh/g) due to a slow tumour elimination half-life, more than 20 h, compared with a plasma elimination half-life of 1.1 to 2-4 h in other tissues such as liver, kidney, spleen or muscle. Half-life in rats was comparable to mice (1.5 l/kg). In beagle dogs, a larger volume of distribution (9 l/kg) was seen.

Distribution studies with radiolabelled docetaxel have showed that is rapidly distributed in tissue, especially into liver, bile, intestine and gastric contents. It was also distributed to spleen, myocardium, bone marrow, pancreas and salivary gland. It was detected as well in foetal tissue and milk. Low levels of docetaxel were detected in brain; however penetration can be increased by inhibition of p-glycoprotein.

In vitro binding to plasma proteins has been found high in mouse (89-95%), rat (70-76%), dog (83-89%) and human (90%). In human plasma was mainly bound to albumin and α1-acid glycoprotein. *In vivo* plasma protein binding was also high.

Several studies have shown that hepatic metabolism and biliary excretion are the major elimination pathway of docetaxel in all species. Only a minor fraction of the dose was excreted in the form of uncharged parent drug. Studies in rat and human liver microsomes have indicated that the CYP3A subfamily is the main responsible for docetaxel biotransformation. Further studies have demonstrated that cytochrome P450 3A4 and 3A5 were the most active for the oxidation of docetaxel to the primary

metabolite RPR104952 and for subsequent oxidation of RPR104952 to RPR111059 and RPR 111026. All four of the principal metabolites of docetaxel have greatly reduced cytotoxic activity against cancer cell lines *in vitro* and *in vivo*.

Faecal excretion has been shown to account for more than 80% of the dose and occurred mainly during the first two days. Recovery of radioactivity after 7 days was >95% in mice, >85% in rats and >90% in dogs. Urinary excretion was low (<10%).

Drug Interactions

Docetaxel is a substrate of CYP3A liver enzymes, therefore its metabolism may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by cytochrome P450-3A. *In vitro* studies have showed that ketoconazol, midazolam, erythromycin, testosterone, orphemnadrine and troleandomycin, inhibitors of CYP3A, reduced docetaxel metabolism. No interactions were observed with cisplatin, doxorubicin, vincristine and vinblastine.

Further studies *in vivo* have shown that ritonavir inhibited docetaxel metabolism. Ranitidine and diphenhydramine, metabolized by CYP3A, did not alter docetaxel metabolism. Synergistic inhibition of tumour growth in breast and colorectal cancer has been observed when docetaxel was given in combination with capecitabine. The combination of sunitinib and docetaxel and the combination of sunitinib, docetaxel and cetuximab showed additive effects.

No interaction have been observed when dexamethasone was administered s.c. simultaneously with docetaxel i.v. to mice. Neverthelss, COX-2 inhibitors enhanced the activity of docetaxel *in vitro* and *in vivo* in several studies.

The most toxic was the combination of docetaxel and cisplatin, while the least toxic was the combination with vinca alkaloids.

Toxicology

Single-dose toxicity

Results for single-dose toxicity studies are summarised in table 3.

Table 3. Single dose toxicity studies in mice, rats and dogs (dose in mg/m^2).

Parameter	Mouse	Rat	Dog
TDL [a]	NA [e]	NA	15
HNTD [b]	<285	<60	<15
HNLD [c]	285	60	30
LD_{10}	345	NA	NA
LD_{50}	414	NA	NA
LD [d]	≥ 414	240	≥ 50

[a] Toxic dose low, [b] Highest non-toxic dose, [c] Highest non-lethal dose, [d] Lethal dose, [e] Not applicable

Studies in mice have showed that the main toxicity effects were seen on haematopoietic parameters, neurotoxicity (doses ≥ 144 mg/m^2) and testicular atrophy (doses ≥ 285 mg/m^2).

In rats, mortality was seen at doses ≥ 120 mg/m^2. Main toxic effects were alopecia and testicular atrophy (doses ≥ 120 mg/m^2) and hematopoietic toxicity (doses ≥ 60 mg/m^2). Abnormal mitosis and single cell necrosis was observed 4 days after treatment but disappeared 29 days after. However, in dogs doses of 30 mg/m^2 caused moderate diarrhoea and white blood cell reduction.

In monkeys, single doses of 50 mg/m^2 produced leukopenia and gastrointestinal effects.

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.