07 July 2011
EMA/586425/2011
Patient Health Protection

Assessment report for Docetaxel Teva Generics and associated names

Pursuant to Article 29(4) of Directive 2001/83/EC, as amended

International Non-proprietary Name: docetaxel

Procedure No. EMEA/H/A-29/1277

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

1. Background information on the procedure

1.1. Decentralised procedure (DCP) and CMD(h) 60 day procedure

Teva Generics B.V. submitted an application for decentralised procedure of Docetaxel Teva Generics, docetaxel 20 mg and 80 mg, powder and solvent for solution for infusion.

The application was submitted to the reference Member State (RMS): The Netherlands and the concerned Member States (CMS) : Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia, Malta, Norway, Poland, Romania, Sweden, Slovenia, Slovak Republic, United Kingdom.

The Decentralised procedure NL/H/1608/001-002/DC started on 30 January 2009.

On day 210, Sweden and Germany major issues on bioequivalence, remained unsolved; hence the procedure was referred to the CMD(h), under Article 29, paragraph 1 of Directive 2001/83/EC, as amended, by the Netherlands on 20 May 2010. The CMD(h) 60 day procedure was initiated on 31 May 2010.

Day 60 of the CMD(h) procedure was on 29 July 2010 and since there could be no agreement the procedure was referred to the CHMP.

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC as amended, to the CHMP was made by The Netherlands on 30 July 2010. Sweden and Germany raised public health objections since the composition of Docetaxel Teva Generics is not equivalent to the reference medicinal product as a different excipient is used, and the difference in composition is too pronounced for a conclusion that this difference may not have an impact in vivo; differences in release characteristics and in vivo pharmacokinetic profile. The data presented by the Applicant was not considered to be sufficient for Docetaxel Teva Generics.

2. Scientific discussion during the referral procedure

2.1. Introduction

Docetaxel (N-Debenzoyl-N-tert-butoxycarbonyl-10-deacetyltaxol) is a semi-synthetic taxane with cytotoxic anti-neoplastic activity. It is highly lipophilic and practically insoluble in water.

Docetaxel promotes the assembly of tubulin into stable microtubules and furthermore it inhibits the microtubules' disassembly, thus interfering with the microtubule network in cells (demonstrated in vitro), which is essential for mitotic cell division and other vital cellular functions. Consequently, docetaxel is assumed to inhibit cellular proliferation and to induce apoptosis.

Since the pharmaceutical form of Docetaxel Teva Generics (powder for solution for infusion) differs from the reference product (concentrate for solution for infusion) a hybrid application marketing authorisation application (MAA) for Docetaxel Teva Generics 20 mg / 80 mg, powder and solvent for solution for infusion, 20 mg and 80 mg was submitted, in accordance with Directive 2001/83/EC, article 10(3).

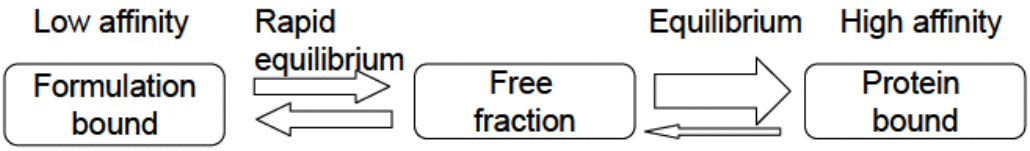
The reference product is Taxotere, concentrate and solvent for solution for infusion (20 mg and 80 mg), by Sanofi-Aventis France. This reference product was approved through the centralised procedure and has been marketed in Europe since November 1995.

The formulation of Docetaxel Teva Generics is not the same as the reference product as a different excipient is used. The reference formulation contains polysorbate 80 as excipient, while the generic formulation contains povidone K12, hydroxypropylbetadex (HP-b-CD) and glucose monohydrate as excipients.

The function of the excipients polysorbate 80 in Taxotere, and of HP-b-CD and povidone K12 in Docetaxel Teva Generics, is to solubilise docetaxel to produce a solution for infusion that is stable on storage, and to protect against the active compound sticking to container walls or precipitating during storing, during the dilution into an infusate, and during the initial infusion procedure. Following infusion, the active ingredient and excipients are highly diluted in the patient's plasma.

The following data has been provided by the Applicant:

- Molecular modelling data describing relative weak affinity for hydroxyl-propylbeta-cyclodextrin (HP-b-CD), and high binding affinity for plasma proteins, indicating that plasma protein binding will be the driving force for distribution of docetaxel in the bloodstream, with only minor – if at all- effect of HP-b-CD (see Figure below).



- In vitro protein binding data submitted during the initial procedure indicated that protein binding of docetaxel is similar for Docetaxel Teva Generics and Taxotere. The Applicant provided additional, more elaborate protein binding data, and these data indicate that the dissociation pattern and protein binding is similar at clinically relevant concentrations.
- Supportive PD and PK data were obtained from animal models: these data indicate comparability with respect to PK (rat, monkey), PD and toxicological parameters.

Excipients povidone K12 and HP-b-CD are known, and the assumption that no safety issues are expected is supported by animal data. The assessment is in line with earlier applications for generic docetaxel products.

The RMS was of the view that based on the in vitro protein binding data provided by the Applicant, no differences with respect to unbound and protein bound docetaxel after infusion are expected. This assumption is supported by the provided animal data. All data considered collectively were thought to strongly suggest comparable docetaxel exposure obtained from Taxotere and Docetaxel Teva Generics. The 'generic' principle is that under those conditions of comparable exposure, no difference in efficacy and active substance (docetaxel)-related safety is expected. In this respect it was the RMS's view that, the fact that a different methodology was applied to avoid docetaxel precipitation in the infusion bag (i.e., using HP-b-CD aggregates and povidone K-12 in case of Docetaxel Teva Generics instead of polysorbate micelles in case of Taxotere), does not impair this conclusion of comparable efficacy, since this conclusion is based on the final exposure of the identical active substance –docetaxel, in both formulations.

With regard to safety related to the excipients, it was considered by the RMS that the different excipients povidone 12 and HP-b-CD are being used in other medicinal products for intravenous use, and thus have been applied in humans. The lack of safety issues caused by these excipients was also supported by animal data. The RMS was therefore of the view that the in vitro data provided, supported by the animal PK and PD data, are sufficient to demonstrate a comparable in vivo behaviour.

However according to the objecting CMS, the in vitro data provided were insufficient to demonstrate similar in vivo behaviour. Concerns were expressed that the formulations (cyclodextrin complexes vs. traditional micelles) are different, and that this generic docetaxel formulation had never been given to man.

Some CMS however, argued that an additional human bioequivalence study (BE) is unlikely to provide critical new data which would not be available from currently conducted animal (rat and monkey) pharmacokinetic studies. This position was endorsed by the RMS.

At the end of the CMDh procedure the objecting CMSs were of the view that the application is not approvable since potential serious risks to public health still remain:

The micelle forming polysorbate used in the originator is exchanged for a cyclodextrin derivative in Docetaxel Teva Generics, which has a different form of interaction with the drug substance. Since the formulation of Docetaxel Teva Generics is different from the originator, different release characteristics and in vivo pharmacokinetic profile cannot be ruled out. The difference in composition is too pronounced for a conclusion that this difference may not have an impact in vivo. The data presented by the applicant was not considered to be sufficient to claim similarity, and as this is a new complex formulation clinical data was considered to be necessary. To conclude, an approval could not be recommended unless the applicant could demonstrate comparable PK-profiles in vivo in man. Until now, no study in man has been conducted with this new formulation. An additional benefit of a bioequivalence study prior to marketing authorisation would thus be that such a study would provide at least some reassurance with respect to safety.

2.2. Critical evaluation

Since the formulation of Docetaxel Teva Generics is not equivalent to the originator Taxotere (as a different excipient) is used, a List of Questions (LoQ) was addressed to the Applicant. The responses received from the Applicant were assessed and are summarised below:

1. The applicant should justify why the provided in vitro data and supporting non-clinical PK studies are sufficiently reassuring for comparable release characteristics of unbound docetaxel of Docetaxel Teva Generics and Taxotere to waive a bioequivalence study in vivo in man.

The Applicant argued that the formulations used in both Teva Docetaxel and Taxotere are not designed to control release or disposition, they are intended to be administered at the same rate, and neither have been shown to affect the disposition of the drug substance as supported by comparative rat and monkey PK data. The physico-chemical properties of the two products do differ, but despite the use of different excipients that dissolves docetaxel in different ways, Teva Docetaxel releases docetaxel in a manner that has been characterised to be equivalent to that for Taxotere, in a dilution experiment performed at clinically relevant concentrations in vitro. Reasoned arguments based on literature data to explain why this is the case have also been provided.

The Applicant therefore argued that a biowaiver is then justified on the grounds that Teva Docetaxel fulfils reasonable demands for characterisation of a similar micellar drug behaviour, although by a different mechanism than the originator.

The CHMP acknowledged that the purpose of both solubilizing systems, the excipients polysorbate 80 in Taxotere, and of HP-b-CD and povidone K12 in Docetaxel Teva Generics is to solubilize docetaxel to produce a solution that is stable on storage, and to protect against the active compound sticking to container walls or precipitating during storing, during the dilution into an infusate, and during the initial infusion procedure. Thereafter, following infusion, the active ingredient and excipients are highly

diluted in the patient's plasma and the docetaxel component is rapidly equilibrated with binding plasma proteins. This rapid equilibration will sequester the active on infusion. The CHMP also agreed with the applicant's statement that "the formulations used in both Teva Docetaxel and Taxotere are not designed to control release or disposition, they are intended to be administered at the same rate, and neither have been shown to affect the disposition of the drug substance as supported by comparative rat and monkey PK data".

Based on the in vitro protein binding data provided by the Applicant, no differences with respect to unbound and protein bound docetaxel after infusion are expected. This assumption is supported by the provided animal data. All data considered collectively, suggest comparable docetaxel exposure obtained from Taxotere and Docetaxel Teva Generics. The 'generic' principle is that under those conditions of comparable exposure, no difference in efficacy and active substance (docetaxel)-related safety is expected.

The excipients povidone K12 and HP-b-CD are not known to cause safety problems as supported by animal data and intravenous use in other medicinal products.

In this respect, the fact that a different methodology was applied to avoid docetaxel precipitation in the infusion bag, i.e., using HP-b-CD aggregates and povidone K-12 in case of Docetaxel Teva Generics instead of polysorbate micelles in case of Taxotere, is not considered to impair this conclusion of comparable efficacy, since this conclusion is based on the final exposure of the identical active substance –docetaxel- in both formulations.

2. The applicant should justify why there is no need for a study in man to provide reassurance with respect to safety of Docetaxel Teva Generics.

The Applicant argues that the general benefit and risk properties of docetaxel treatment is well known, and no safety concern has been identified with the Teva docetaxel drug substance. Furthermore it has been described, from literature and from the Applicant's own experiments, why Teva docetaxel is not likely to yield higher exposures than the originator product: the high protein binding of docetaxel makes this proposition virtually impossible by it's capacity to sequester the active docetaxel on infusion, and the in vitro measurements of free fraction on dilution supports this notion. Also in an acute toxicity study in the rat, there was no indication that the Teva docetaxel product should be more toxic than Taxotere.

The CHMP acknowledges that the release of docetaxel from formulation to binding proteins was found indistinguishable between Taxotere and Docetaxel Teva Generics in experiments performed at clinically relevant dilutions. Since docetaxel binds to plasma proteins with a high capacity and a firm binding affinity that is stronger than the affinity for the formulation constituents, both formulations are argued to be equivalent with respect to the pharmacodynamic active docetaxel. This assumption is supported by the provided animal data. All data have been considered collectively by the CHMP.

Furthermore, the safety of docetaxel is well known and no new safety concerns are expected with the Teva product. With regard to the safety related to the excipients povidone K12 and HP-b-CD it has already been stated in the previous question that these are used in other medicinal products for human intravenous use, and that these are not known to cause safety problems.

3. The applicant should justify why the provided data are sufficiently reassuring for comparable uptake in pharmacological (tumours) and toxicological target tissues of docetaxel of Docetaxel Teva Generics and Taxotere with a focus on the time-dependent relative quantity of different forms of docetaxel in plasma (e.g. formulation bound, free, protein bound) and the effects of differences (if any) on distribution of docetaxel in an organism.

The purpose of docetaxel treatment is to kill tumour cells. This is brought about by a mechanism that needs to be active over a sufficient time span to have a reliable effect on cell division. Docetaxel is known to be schedule independent, and intracellular levels are built up over time. Also toxicological effects are mainly expected to be exposure/AUC-dependent.

Concerning the degree of reassurance provided by the data, the Applicant highlights the following observations:

- This, and previous, questions have focused on potential formulation impact on free plasma levels in the transient period around the time of infusion.
- We have not been able to find any significant differences in protein binding between properties with the two formulations at clinically relevant concentrations and, also over a wide range of dilutions that mimics the kinetic changes that occur with time when the products are infused in the blood stream.
- In addition, initial free plasma levels may have less impact on subsequent re-distribution to target organs in view of the high plasma protein binding that will re-equilibrate with extravascular structures over time.
- The excipients are rapidly removed, possibly before maximum intracellular concentrations of docetaxel are attained.
- And there were no real differences in animal models to study efficacy and safety, although these were admittedly not powered for formal comparative purposes.

I

While the critical aggregate concentration CAC of HP-b-CD aggregates in plasma has not been directly characterised it is assumed to be at least as high as CAC in aqueous solution, 54 mg/ml (Duan et al, 2005[1]), in analogy with the findings for PS80 CMC discussed above.

In addition to the Cmax for the HP-b-CD being below CAC, and for PS80 below CMC, respectively, a significant amount of free docetaxel will be driven out of the respective aggregate systems through rapid and strong binding to plasma protein during infusion. Therefore, polysorbate micelles and HP-b-CD aggregates are immediately disintegrated during and shortly after infusion.

The Applicant therefore concludes that from available data, the presence of micelles (or complexes (aggregates)) used in these products do not by themselves influence the free fraction of docetaxel. Indirect effects through displacement of bound drug from protein may occur, but is not likely to play a major role.

Based on the reported critical aggregate concentration (CAC) and the expected Cmax upon infusion for HP-b-CD, the CHMP considered that it is very unlikely that HP-b-CD aggregates will be present after infusion, and no effect of such aggregates on docetaxel pharmacokinetics is to be expected. In combination with the response on polysorbate 80 in Question 1, the CHMP agrees with the Applicant that it is considered very likely that neither polysorbate 80 micelles nor HP-b-CD aggregates are present in the bloodstream in amounts that would affect docetaxel pharmacokinetics or docetaxel free fraction after infusion of Taxotere or Docetaxel Teva Generics, respectively.

3. The method to determine in vitro protein binding in the dilution experiment involves a centrifugation step which could have an impact on the stability of the micelles, making

[1] Duan MS, Zhao N, Össurardóttir IB, Thorsteinsson T, Loftsson T. Cyclodextrin solubilization of the antibacterial agents triclosan and triclocarban: Formation of aggregates and higher-order complexes. Int. J. Pharm. 2005 Jun 13; 297(1-2): 213-22.

interpretation of the results less reliable. The reliability of the results should be discussed by the applicant.

The Applicant states that the method of using ultrafiltration (UF) to separate bound and unbound docetaxel was validated successfully by Mortier and Lambert, (2006)[2]. Although the effect of centrifugation step was not specifically studied in this study, the above paper well demonstrated the validity of the method.

Moreover, as discussed above, the Applicant argues that polysorbate micelles or HP-b-CD aggregate systems should exist as disintegrated form under the CMC/CAC in plasma, and that therefore, there should be no concern about the stability of micelles at concentrations used in the experiments.

It is also emphasised that all in vitro studies presented have been performed as head-to-head comparisons between Docetaxel Teva Generics and Taxotere, and that no significant differences have been found. The Applicant then assumes that any artefact should affect parameters for both products to a similar extent.

Data obtained by ultrafiltration method show that the fraction of unbound docetaxel for both SID530 (laboratory code for the Teva docetaxel formulation; complex (aggregate) bound) and Taxotere (micellar) stayed between 6 and 7% and the slowly increasing pattern was very similar.

Following the receipt of the LoOIs from CHMP, the Applicant also conducted a protein binding study using the **equilibrium dialysis (ED)** method at high concentrations (0.5 and 1 ug/ml of PS 80). The results showed that the free fraction of docetaxel was consistently similar between Taxotere and SID530 with no statistically significant difference found by Student's T-test.

The CHMP agreed that the protein binding method using the ultracentrifugation step is a validated method, known to provide data on free docetaxel levels that are similar to those obtained using equilibrium dialysis methods. The head-to-head comparisons between Taxotere and Docetaxel Teva Generics indicate no differences in free docetaxel fractions under all relevant concentrations, and this conclusion is even further strengthened by the additionally provided protein binding data, using equilibrium dialysis, that is fully in line with data obtained using the previously used 'ultracentrifugation' methodology. Thus, no difference in free docetaxel levels at clinically relevant dilutions has now been demonstrated using two protein binding methods.

4. The relevance of the non-clinical studies in the assessment of similarity should be discussed by the applicant.

The Applicant claims that the non-clinical studies were referenced as additional data and were intended to support their detailed comparisons in vitro, to ensure that any important factor that could result in significant differences in efficacy or safety, has not been overlooked. The results of the non-clinical tests carried out support the company's position.

The basic and underlying assumption is that if the detailed in vitro protein binding and dilution study data should have missed out any important properties and there would be significant differences in biologically available docetaxel between the two formulations (that were never designed to retain active compound as depots), this would have been reflected at least in the plasma kinetics of the administered drug in animals.

4.1 The relevance of the non-clinical PK-studies should be discussed, taking into consideration the limited number of animals and the uncertainty of whether free or total (including micellar/complex bound) docetaxel was measured.

[2] Mortier KA, Lambert WE. Determination of unbound docetaxel and paclitaxel in plasma by ultrafiltration and liquid chromatography–tandem mass spectrometry. J. Chromatography A 2006; (1108): 195-201.

The pharmacokinetics of Taxotere and Docetaxel Teva Generics were evaluated in 3 studies in rats and monkeys and the concentration of total fraction of docetaxel was determined. The results showed a concentration independent protein binding rate in the plasma concentration range between 0.2 and 2 ug/ml for Taxotere and Docetaxel Teva Generics. According to Urien et al. (1996)[3], the protein binding rate of docetaxel was concentration independent within a clinical relevant range of 1-5 ug/ml.

The two PK studies in rats show small variability and no apparent difference in exposure. In the PK study in monkeys, 90% confidence intervals for AUC and Cmax were within the 80-125 acceptance criterion for human bioequivalence testing. From the 3 animal PK studies, not dimensioned according to human bioequivalence comparison standard, the Applicant claims that they could not find any sign that there are any differences in "disappearance" of active drug from the plasma compartment, to metabolism or tissue re-distribution that would indicate any difference between formulations in biologically available compound.

The main point being highlighted here is not to what extent these pharmacokinetic studies would fulfil "human bioequivalence" criteria, but that they provide an independent support, with a sufficiently high resolution, that the absence of any significant differences in protein binding properties that was found in repeated in vitro studies, is not contradicted by any apparent difference in vivo of compound handling over time.

With respect to the provided animal pharmacokinetic studies, the CHMP supports the Applicant's conclusion. All data provide evidence that no differences in docetaxel levels are obtained between infusion of Taxotere or Docetaxel Teva Generics. Of note, total docetaxel levels were measured in these animal experiments. However, in vitro protein binding of docetaxel was comparable for both formulations and because of the rapid equilibrium between free and protein bound docetaxel, any difference in free docetaxel levels would translate in a difference in total docetaxel.

In fact the rat data can be taken as initial circumstantial evidence that there is no difference in free docetaxel levels present between Taxotere and Docetaxel Teva Generics. Furthermore, the monkey data can be taken as more pivotal data, as the experiment in these larger non-rodents might be considered as an animal model of bioequivalence testing, with the same restrictions regarding the determination of the total concentration as opposed to the free fraction only.

In conclusion, the CHMP accept that these animal data confirm the provided in vitro data, which clearly indicate the absence of any relevant difference in free docetaxel plasma levels, and which forms the basis of the current application.

4.2 The relevance of the non-clinical PD studies and their sensitivity should be discussed taking into account the low number of animals and the accuracy of manual tumour size measurements of ≤3 ml.

Regarding the general relevance and measurement technology of the non-clinical studies, the Applicant makes the following observations starting with the latter:

1) Because the purpose of the pharmacodynamic study was to observe the anti-tumour effect of drug products over time, the measuring of tumour size in vivo, which yields a prompt comparison was thought more appropriate than other staining methods involving sacrifice of animals.

2) The nude mouse model bearing tumour Xenografts is well defined and widely-used animal model in an anti-cancer drug research field and there have been many studies which determine the volume of

[3] Urien S, Barré J, Morin C, Paccaly A, Montay G and Tillement J-P. Docetaxel serum protein binding with high affinity to alpha1-acid glycoprotein. Int. New Drugs 1996; (14): 147-151.

tumour by using a vernier caliper in this animal model. (Williams et al. (2004)[4]; Shaik et al. (2006)[5]). The animal number of 8 for each group was considered adequate since it was within a usual range of animal numbers used in previous studies (n=5-10) and produced a statistically significant comparison between treatment groups, enabling an effective PD evaluation.

3) Regarding accuracy of manual measurement of tumour size, in order to secure the independence and accuracy of the study results, the identical test was carried out twice in two separated institutions; SK Chemicals and Chemon (KGLP). The two independent PD studies had the tumour size between 50 and 700 mm3, and Applicant ensures that the measurement tumour size was considered precise and accurate. Moreover, the inhibition rate of tumour growth was correlated with the changes in tumour weight, supporting the accuracy of the measurement further.

That said, the main issue with the data presented is neither the number of observations, nor tumour size assessment, but the obvious fact that the doses used were too high for high-resolution assays. The effect was at the top end of the dose-response curve where above 80% tumour growth inhibition (or more) was obtained. The Applicant argues that the pharmacodynamic studies in tumour bearing mice, demonstrate that the high doses of both products used, do work as expected and do not contradict the conclusion on similar properties drawn from high resolution in vitro data.

The CHMP considered the pharmacodynamic data with mouse to be supportive in nature; the small variability in the study being impressive. In the assessment of the 'similarity' this result in mice carries the smallest weight. In fact the in vitro data appears to provide the strongest evidence about the equivalence of the free fraction, which is supported with the "bioequivalence" testing in monkeys. The PD data in mice do not contradict this conclusion.

5. Taking the above-mentioned uncertainties into account, the Applicant should clarify why the provided in vitro data are sufficient to alleviate concerns regarding possible differences in free docetaxel fractions during and shortly after infusion of Taxotere and Docetaxel Teva Generics.

The Applicant argues that since adherence to infusion rates recommended in the SPC is to be assumed, it is not likely that overexposure to Docetaxel Teva Generics would be an issue, nor under-dosing. Also no significant differences in free fraction between the two formulations during dilution experiments have been found. Already at 1:10 drug:plasma dilution, there was no difference in free fraction measured, and considering an expected intravenous infusion rate of in the range of 250 mL/h, a 10:1 dilution must occur within seconds.

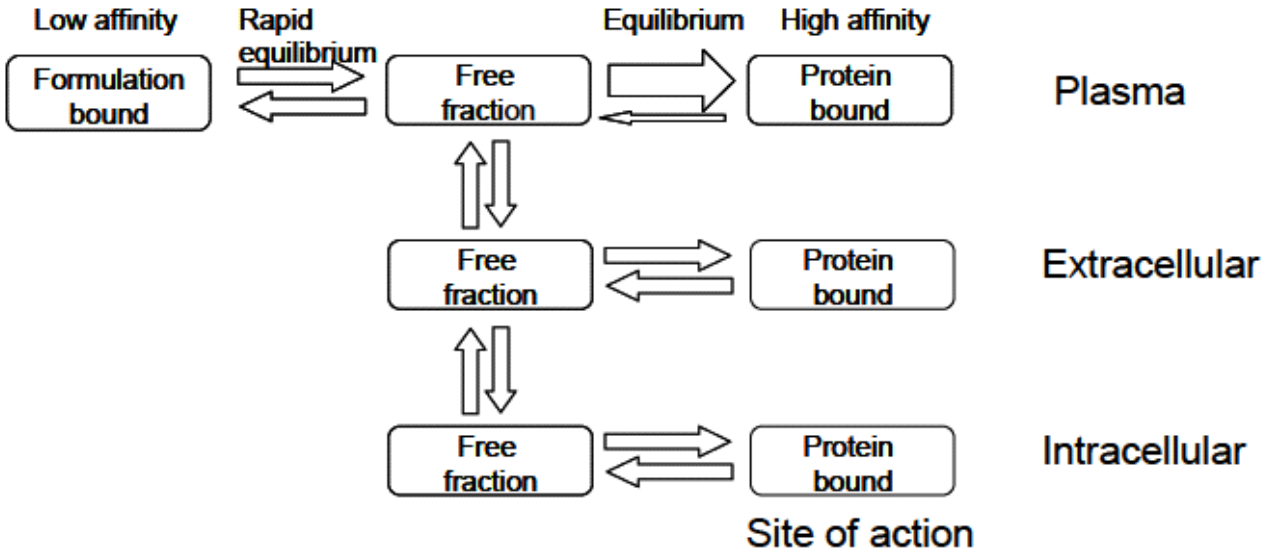
The basic standpoint is that a high affinity and capacity protein binding drives redistribution of active compound to an extent that makes the influence of differences between delivery systems (at least such designed for immediate release within reasonable limits) on free fraction negligible, and the Applicant states that it has repeatedly demonstrated that there are no relevant differences between Docetaxel Teva Generics and Taxotere in this respect.

The Applicant also notes that the recent EMA draft Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (non-polymeric surfactants) actually capture aspects of their arguments: the rapid transfer of free drug out of micellar system due to a binding force to proteins; a passive dissolution of free drug by the greatly increased volume of water outside of the restricted and confined vascular compartment

[4] Williams KJ, Telfer BA, Brave S, Kendrew J, Whittaker L, Stratford IJ, Wedge SR. ZD6474, a potent inhibitor of vascular endothelial growth factor signalling, combined with radiotherapy: schedule-dependent enhancement of anti-tumour activity. Clin Cancer Res. 2004 Dec 15;10(24):8587-93.
[5] Shaik MS, Chatterjee A, Jackson T, Singh M. Enhancement of anti-tumour activity of docetaxel by celecoxib in lung tumours. Int. J. Cancer. 2006 Jan 15;118(2):396-404.

without exceeding the solubility limit; a partitioning of free drug into the many lipophilic domains in the body without exceeding the solubility limit.

Also, in relation to efficacy, the applicant notes that the anti-tumour effect of docetaxel is schedule independent and obtained at site(s) somewhat remote to the plasma pharmacokinetics compartment(s). A more realistic version that also captures the intervening buffering capacity of the biological system is shown in the figure below.



The applicant argues that that such a system of coupled equilibria would be expected to dampen out any transient variation in free fraction.

The CHMP agrees that the basic principle of a high affinity and capacity protein binding driven distribution of docetaxel, resulting in irrelevant effects of polysorbate 80 micelles on the free docetaxel levels is supported. It is further agreed that in vitro data clearly indicate that no differences in free docetaxel levels will exist between Taxotere and Docetaxel Teva Generics.

2.3. Conclusions and benefit risk assessment

A special feature for generic Docetaxel formulations is that, although it is given as an intravenous solution, systemic exposure from the innovator and generic preparation is not a priori assumed to be identical. Instead, for this kind of application, the need for additional data to be provided by the Applicant to support the presumed identical systemic exposure was one of the main points of discussion by the CHMP. This additional requirement is due to the presence of polysorbate 80 in the Taxotere formulation, by which docetaxel pharmacokinetics may be affected. It was argued that the purpose of additional data was to assure that the excipients (be it another micelle forming agent or another type of solubilser) do not result in differences in systemic exposure to the active ingredient docetaxel. When sufficient reassurance of identical behaviour and pharmacokinetics is provided, based on the 'generic principle', efficacy and safety of Taxotere and Docetaxel Teva Generics is deemed to be identical as well.

Indeed, in vitro protein binding data submitted during the initial procedure, CMD(h) referral procedure and the current CHMP referral procedure indicated that the dissociation pattern and protein binding is similar for docetaxel from Docetaxel Teva Generics and Taxotere at clinically relevant concentrations, and thus systemic exposure to docetaxel is expected to be the same. Supportive pharmacokinetic (PK), and to a limited extent pharmacodynamic (PD), data were obtained from animal models, and indicate

comparability with respect to docetaxel pharmacokinetics (rat, monkey), pharmacodynamics and toxicological parameters.

The main point for discussion was if the free fraction immediately after infusion of Taxotere and Docetaxel Teva Generics is the same, and whether the docetaxel is released at a sufficiently equal rate from the Taxotere micelles and the Docetaxel Teva Generics HP-b-CD. Furthermore, the robustness of the provided animal data, and the level of extrapolation from the in vitro data to the in vivo situation was questioned.

The Applicant discussed these issues in their responses to the Referral LoOI, as discussed below:

- The proposed formulation is adequately justified (aimed at obtaining comparable exposure to docetaxel).
- Pharmaceutical quality of Docetaxel Teva Generics is comparable to that of Taxotere.
- Molecular modelling data describing the relative weak affinity for HP-b-CD, and high binding affinity for plasma proteins, indicate that plasma protein binding will be the driving force for distribution of docetaxel in the bloodstream, with only minor – if at all- effect of HP-b-CD (see Figure above). According to the CHMP, it is considered demonstrated that docetaxel in the Docetaxel Teva Generics formulation is surrounded by a number of cyclodextrin molecules, so is an exclusion complex rather than an inclusion complex, with weak interaction forces expected between the docetaxel and cyclodextrin molecules.
- In vitro protein binding data submitted during the initial procedure, CMD(h) referral procedure and the current CHMP referral procedure indicated that the dissociation pattern and protein binding is similar for docetaxel from Docetaxel Teva Generics and Taxotere at clinically relevant concentrations.
- In the second round of this Referral, it was made clear that it is very unlikely that polysorbate 80 micelles remain present for 3 hours after infusion of Taxotere, with possible effect on Docetaxel pharmacokinetics. The Applicant provided compelling arguments that the CMC in plasma is much higher than the often reported CMC in water of 0.012 mM. This increased CMC makes it less likely that polysorbate micelles are indeed present in the blood stream, even very shortly after infusion. Moreover, polysorbate 80 micelles are very unstable and will disappear rapidly due to hydrolyses and metabolism by plasma carboxyesterases. Published data show that the concentration of polysorbate 80 following infusion of Taxotere in actual patients falls down to below the CMC in plasma immediately during infusion. Therefore, the putative increased free docetaxel fraction by polysorbate 80 micelles does not appear to be present, and thus not relevant for the actual situation.
- The absence of a relevant effect is in line with in vitro data obtained within this application, where in a head to head comparison no difference in free docetaxel in relation to dilution factors was observed for Taxotere, and the same lack of effect was observed for Docetaxel Teva Generics. The results of the in vitro studies can now be considered in line with current expectations based on thorough evaluation of the available physicochemical data on this subject, as provided in the responses to the referral LoOI.
- Supportive PD and PK data were obtained from animal models, and indicate comparability with respect to docetaxel pharmacokinetics (rat, monkey), pharmacodynamics and toxicological parameters.
- The excipients povidone K-12 and HP-b-CD that are used in Docetaxel Teva Generics, but are not used in Taxotere, are known from other medicinal products, and no safety issues are expected. This assumption is also supported by animal data.

- The assessment for this Docetaxel Teva Generics is in line with earlier applications for generic docetaxel products, where known but different excipients were applied.

The applicant was invited to attend an oral explanation before the CHMP on the 15 February 2011 to defend their position with respect to their arguments presented in their responses.

One of the points highlighted by the applicant was that the Loos data reviewed do not support changes in free fraction over a clinically relevant concentration range in vitro. Further evidence was also presented that the clinical data on free fraction during infusion do not support any transient effects on free fraction (Acharya et al., 2004).

However taking into account the literature data presented by the applicant, it was noted by some members of the CHMP that according to the data by Wang et al (2010), the CMC of PS 80 in human plasma protein concentration was not substantially greater than the clinically relevant range of post-infusion levels of PS 80 (from Taxotere) reported by Webster et al (1997). The necessity of human data was also discussed – focussing on at least the first 3 hours, since in vitro data does not predict the rate of release in human blood.

Nevertheless taking into account all the information available in the case of Docetaxel Teva Generics, i.e the applicant's data, the evidence from literature submitted in support, as well the arguments presented at the oral explanation, the CHMP considered that sufficient reassurance is provided by the applicant that systemic exposure to the active ingredient between the innovator Taxotere and Docetaxel Teva Generics is the same, and therefore safety and efficacy related to docetaxel will be the same as well, and thus was of the view that the risk-benefit balance for Docetaxel Teva Generics is positive.

2.4. Recommendation

Based on the in vitro protein binding data provided by the Applicant, no differences with respect to unbound and protein bound docetaxel after infusion are expected. This assumption is supported by the provided animal data. All data considered collectively, strongly suggest comparable docetaxel exposure obtained from Taxotere and Docetaxel Teva Generics. The 'generic' principle is that under those conditions of comparable exposure, no difference in efficacy and active substance (docetaxel)-related safety is expected.

In this respect, the fact that a different methodology was applied to avoid docetaxel precipitation in the infusion bag, i.e., using HP-b-CD aggregates and povidone K-12 in case of Docetaxel Teva Generics instead of polysorbate 80 micelles in case of Taxotere, does not impair this conclusion of comparable efficacy, since this conclusion is based on the final exposure of the identical active substance – docetaxel- in both formulations.

With regard to safety related to the excipients, it was additionally considered that the different excipients povidone K-12 and HP-b-CD are used in other medicinal products for intravenous use, and thus have been applied in humans. The lack of safety issues caused by these excipients also was supported by animal data.

2.5. Conclusions and Benefit Risk assessment

Therefore the CHMP considered that the risk-benefit balance for Docetaxel Teva Generics to be favourable.

Based on:

- The in vitro protein binding data point at comparable docetaxel exposure obtained from Taxotere and Docetaxel Teva Generics;
- This assumption is supported by the non-clinical animal data;
- With regard to safety related to the excipients, it was considered that the different excipients povidone K-12 and HP-b-CD are used in other medicinal products for intravenous use, and thus have been previously applied in humans;

The CHMP was of the opinion that the benefit/risk ratio of Docetaxel Teva Generics is considered to be favourable. The CHMP issued a positive opinion recommending the granting of the marketing authorisation and of the summary of product characteristics, labelling and package leaflet as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.