Annex II

Scientific conclusions and grounds for positive opinion presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of Docetaxel Teva Generics (see Annex I)

Docetaxel (N-Debenzoyl-N-tert-butoxycarbonyl-10-deacetyl taxol) is a semi-synthetic taxane with cytotoxic anti-neoplastic activity. Since the pharmaceutical form of the 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 an 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.

During the decentralised procedure the reference member state (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 K12 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 concerned member state (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.

The objecting CMSs argued that the formulation of Docetaxel Teva Generics is not equivalent to the originator as a different excipient is used. 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.

The aim of the assessment has been to clarify if systemic exposure to docetaxel from Taxotere and Docetaxel Teva Generics is equal. It is assumed that if sufficient reassurance is provided that systemic exposure to the active ingredient between the innovator Taxotere and Docetaxel Teva Generics is the same, then safety and efficacy related to docetaxel will be the same as well. Therefore the main point for discussion was whether 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 assessed.

The Applicant discussed these issues in their responses to the Referral List of Outstanding Issues (LoOI), as discussed below:

- The proposed formulation is adequately justified (aimed at obtaining comparable exposure to docetaxel, whereas no improved benefit-risk is claimed by the Applicant)
- 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. According to the QWP, 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 critical micelle concentration (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 et al 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 polysorbate 80 in human plasma protein concentration was not substantially greater than the clinically relevant range of post-infusion levels of polysorbate 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 majority of the CHMP was of the view that sufficient reassurance is provided by the applicant that systemic exposure to the active ingredient between the innovator Taxotere and Docetaxel Teva Generics indeed is the same, and therefore safety and efficacy related to docetaxel will be the same as well. Therefore the risk-benefit balance for Docetaxel Teva Generics is positive.

Grounds for positive opinion

Whereas

- 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 has recommended the granting of the marketing authorisation for which the summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III for Docetaxel Teva Generics and associated names (see Annex I).