Annex II

Scientific conclusions

Scientific conclusions

An application was submitted under the decentralised procedure for Paclitaxel Hetero, 6 mg/mL, concentrate for solution for infusion on 15 May 2014.

The application was submitted to the reference Member State (RMS): Portugal and the concerned Member States (CMS): Germany, Netherlands and United Kingdom.

The decentralised procedure PT/H/1256/001/DC started on 04 June 2014.

On day 210, major issues on bioequivalence, raised by the Netherlands, remained unresolved; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1 of Directive 2001/83/EC, by Portugal on 02 November 2017. In the meantime, the applicant withdrew the application in the Netherlands. The CMDh 60 day procedure was initiated on 29 January 2018.

Day 60 of the CMDh procedure was on 29 March 2018 and as no agreement could be reached the procedure was referred to the CHMP.

On 29 March 2018 Portugal therefore triggered a referral under Article 29(4) of Directive 2001/83/EC. The Netherlands raised objections on the fact that the indirect comparison data on which the applicant based its claim for equivalence was not considered robust nor was convincing enough to support a biowaiver, and this was regarded to be a potential serious risk to public health.

Overall summary of the scientific evaluation by the CHMP

The reference medicinal product (Taxol) has a complex formulation for which it is known that the micellar formulation affects the pharmacokinetic profile of paclitaxel after intravenous administration. In such case, in principle a biowaiver of *in vivo* bioequivalence study is only possible when there are adequate *in vitro* data to demonstrate similarity between generic and reference medicinal product.

While there may be occasions where an indirect comparison may be acceptable to support a biowaiver, having assessed the literature provided, the CHMP concluded that the data was not sufficiently robust nor convincing enough to replace the need for a head-to-head comparison using identical methods and performed at the same time for test and reference product, and therefore should be understood as supportive only.

The applicant submitted a study report with results of the direct comparison of micelles' characteristics of Paclitaxel Hetero and Taxol and another publication containing data on the free drug fraction of Taxol in human plasma. However, the additional data provided were not robust enough to establish equivalence between Paclitaxel Hetero and the EU reference medicinal product. The CHMP considered that it is essential in order to waive the bioequivalence study requirement to establish that the generic medicinal product and the reference medicinal product have the same behaviour in plasma and ultimately in vivo, i.e. a direct comparison of the free fraction between the two medicinal products should be considered in line with the "*Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems*" (EMA/CHMP/QWP/799402/2011

The CHMP considered, as a consequence, that the benefit-risk balance of Paclitaxel Hetero is not favourable.

Grounds for the CHMP opinion

Whereas

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC.
- The Committee considered the totality of the data submitted by the applicant in relation to the objections raised as potential serious risk to public health.
- The Committee considered that the data available was insufficient to establish equivalence between Paclitaxel Hetero and the EU reference medicinal product.

The Committee, as a consequence, considers that the benefit-risk balance of Paclitaxel Hetero is not favourable.

Therefore, the Committee recommends the refusal of the marketing authorisation of Paclitaxel Hetero in the reference and concerned Member States.