18 October 2018
EMA/813213/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Paclitaxel Hetero and associated names

INN: paclitaxel

Procedure number: EMEA/H/A-29(4)/1466

Note:

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

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1. Background Information

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 regarded to be a potential serious risk to public health.

2. Scientific discussion

2.1. Introduction

About the product

Paclitaxel Hetero is a concentrate for solution for infusion 6 mg/mL, from Hetero Europe S.L. Viladecans (Barcelona), Spain.

The active substance, paclitaxel, is an antimicrotubule agent that primarily exerts its effect by binding to the β-tubulin subunit in microtubules, preventing depolymerisation and increasing their stability and rigidity. This leads to enhanced polymerization, cell cycle arrest and enhanced apoptosis of proliferating cells. *In vitro*, paclitaxel exhibits cytotoxic activity against a wide variety of both human and rodent tumour cell lines including leukaemia, non-small cell lung carcinoma, small cell lung carcinoma, colon carcinoma, CNS carcinoma, melanoma, renal carcinoma, ovarian carcinoma and breast carcinoma.

Proposed indications

The proposed indications for Paclitaxel Hetero 6 mg/mL, concentration for solution for infusion, are:

Ovarian carcinoma:

- In the first-line chemotherapy of ovarian cancer for patients with advanced carcinoma of the ovary or with residual disease (>1cm) after initial laparotomy, in combination with cisplatin.
- In the second-line chemotherapy of ovarian cancer for the treatment of metastatic carcinoma of the ovary after failure of standard, platinum-containing therapy.

Breast carcinoma:

- In the adjuvant setting, Paclitaxel is indicated for the treatment of patients with node-positive breast carcinoma following anthracycline and cyclophosphamide (AC) therapy. Adjuvant treatment with Paclitaxel should be regarded as an alternative to extended AC therapy.
- Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who overexpress human epidermal growth factor receptor 2 (HER-2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable.
- As a single agent, Paclitaxel is indicated for the treatment of metastatic carcinoma of the breast in patients who have either failed or are not candidates for standard, anthracycline-containing therapy.

Advanced non-small cell lung carcinoma

Paclitaxel, in combination with cisplatin, is indicated for the treatment of non-small cell lung carcinoma (NSCLC) in patients who are not candidates for potentially curative surgery and/or radiation therapy.

AIDS-related Kaposi's sarcoma

Paclitaxel is indicated for the treatment of patients with advanced AIDS-related Kaposi's sarcoma (KS) who have failed prior liposomal anthracycline therapy. Limited efficacy data support this indication.

Regulatory background

Paclitaxel Hetero 6 mg/mL, concentrate for solution for infusion, has been initially submitted through the decentralised procedure with Portugal as RMS (PT/H1256/001/DC) as an abridged (generic) application, according to article 10(1) of Directive 2001/83/EC. The reference medicinal product is Taxol 6 mg/ml concentrate for solution for infusion registered in Portugal by Bristol-Myers Squibb Farmacêutica Portuguesa, S.A., and authorized in the European Union since 20 September 1993. Taxol is a complex/micellar formulation.

According to Article 10(2)(b) of Directive 2001/83/EC, a generic medicinal product is defined as a medicinal product that has:

- the same qualitative and quantitative composition in active substance(s) as the reference medicinal product,
- the same pharmaceutical form as the reference medicinal product,
- and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

In the application for Paclitaxel Hetero, no bioequivalence study with the reference medicinal product Taxol was provided. The applicant stated at the time of the decentralized procedure that Taxol was not available on the European market and thus claimed that neither a bioequivalence nor direct *in vitro* comparison could be made with the reference medicinal product.

The applicant used publically available data[1] obtained with Taxol (published data) in order to perform an *in vitro* comparative characterization, 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).

[1] Scripture CD, Szebeni J, Loos WJ, Figg WD, Sparreboom A. Comparative in vitro properties and clinical pharmacokinetics of Paclitaxel following the administration of Taxol and Paxene. Cancer Biology & Therapy, 2005, 4:555-560.

- **Comparison test *vs.* reference medicinal product**: relevant information on micelle characterisation and pharmacokinetic data of the reference medicinal product (**Taxol**) was provided and discussed regarding its similarity with the test product.
- **Comparison test *vs.* generic product:** the *in vitro* data obtained from comparison of the micellar systems between test product and another generic formulation by **Hospira** (Germany) previously submitted is regarded only as additional information in support of the biowaiver request.

Although the comparative *in vitro* studies versus Paclitaxel Hospira covered the requirements of the *Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems* (EMA/CHMP/QWP/799402/2011) for generic and reference medicinal products having 'similar' composition, the use of another generic product as reference medicinal product could not be accepted by The Netherlands and the following question was raised by the CMDh as a potential serious risk to public health:

- *The results of comparative in vitro studies submitted versus another generic product (Paclitaxel Hospira) cannot be accepted to demonstrate similarity versus Taxol (the reference product used in this abridged application). The applicant is requested to use the EU reference medicinal product (Taxol) as the reference product to demonstrate comparability in vitro. In case no comparability versus Taxol can be shown via in vitro comparison, in principle a bioequivalence study versus Taxol would be required unless the applicant can justify why no bioequivalence study is needed.*

This was based on the fact that Taxol concerns a complex formulation for which it is clearly known that the micellar formulation affects the PK profile of paclitaxel after intravenous administration (release of paclitaxel and volume of distribution). In such case, in principle a biowaiver of *in vivo* BE study is only possible when there are adequate and dedicated *in vitro* data to demonstrate the similarity (such as head-to-head direct comparison) between generic and reference medicinal product, (i.e. Paclitaxel Hetero and Taxol in this case). The Netherlands considered that this indirect comparison as provided by the applicant with the literature data of Taxol was not robust nor convincing enough to support a biowaiver for Paclitaxel Hetero because:

- The similarity *in vitro* between the Taxol and Paclitaxel Hetero demonstrated indirectly was not reliable without a cross-validation with the methods used in the literature study and in the studies conducted for Hetero.
- It was questionable whether the actual product of Taxol was used in the binding study in literature references.
- There was no information regarding the plasma concentration of the test solutions used in the binding study by the equilibrium dialysis method. In addition, the free vs. bound fractions of paclitaxel were only studied at one concentration level in plasma in literature, whereas it is usually expected a comparison of the free fraction of the active substance at different concentration levels in plasma.

The RMS Portugal did not share this opinion and was of the view that based on the results obtained in the information available in the public domain for Taxol (bibliographic data) versus analytical data for Paclitaxel Hetero and on the results of the comparative analytical data between Paclitaxel Hetero and Paclitaxel Hospira concerning mean size and size distribution of the micellar component, estimated concentration of micellar entities and free vs. solubilized fractions of the active substance, it was possible to conclude that both medicinal products (Taxol and Paclitaxel Hetero) can be considered

similar 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).

2.2. Assessment of the issues raised as a potential serious risk to public health

At the start of the procedure, the applicant was requested by CHMP to further substantiate the claimed equivalence between Paclitaxel Hetero and the EU reference medicinal product (Taxol).

In its response, the applicant included once more its strategy for indirect comparison between Paclitaxel Hetero and the reference medicinal product Taxol:

1. A comparison of the quantitative and quantitative composition of Taxol, based on information available in the public domain;
2. An *in vitro* comparison of Paclitaxel Hetero against an approved product marketed in Germany (Paclitaxel Hospira);
3. An indirect comparison of Paclitaxel Hetero against Taxol, based on the data available in the literature about this formulation.

The composition of Paclitaxel Hetero is similar to that of the EU reference medicinal product Taxol. Both solutions have essentially the same quantitative and qualitative composition, including the surfactant Cremophor which is responsible for micellar formation. The only difference seems to be the additional presence of a small quantity of citric acid in Paclitaxel Hetero as an alternative way of addressing a known stability issue by neutralizing the carboxylate groups available in Cremophor.

Comparative *in vitro* studies between Paclitaxel Hetero diluted in 0.9% sodium chloride and Paclitaxel Hospira suggest that the two formulations are comparable in terms of mean size and size distribution of the micellar component, as well as estimated concentration of micellar entities. Clear differences in the free fraction were seen in the comparative equilibrium dialysis studies between Paclitaxel Hetero and Paclitaxel Hospira. Particularly at low concentrations, the free fraction of Paclitaxel Hetero was considerably higher than the free fraction of Paclitaxel Hospira.

Literature data published for Taxol seems to indicate that Taxol has micelle characteristics comparable to those of Paclitaxel Hetero. However, such comparison against the data available in the literature lacks robustness and should be understood as supportive only, in particular as it is not a head-to-head comparison using identical methods and performed at the same time for test and reference product. Moreover, the clear differences seen in the free fraction between Paclitaxel Hetero and Paclitaxel Hospira in the comparative equilibrium dialysis studies indicate that the same behavior in plasma and ultimately, in vivo cannot be guaranteed.

Considering the availability of Taxol in the EU at that point (sourced from Czech Republic), the applicant submitted during the procedure a study report with results of *in vitro* direct comparison of micelles' characteristics such as micellar size, micellar size distribution, zeta potential and solubilisation capacity of Paclitaxel Hetero and the reference product Taxol. Comparative *in vitro* data on the free fraction in plasma, which is a key parameter, between Paclitaxel Hetero and Taxol was nevertheless still not available.

In order to further substantiate its claim, the applicant submitted another publication[2] 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

[2] Brouwer E, Verweij J, De Bruijn P, Loos WJ, Pillay M, Buijs D, Sparreboom A. Measurement of fraction unbound paclitaxel in human plasma, Drug Metab Dispos, 28:1141-5, 2000.

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).

3. Benefit-risk balance

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.

4. Grounds for 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.