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Committee for Medicinal Products for Human Use (CHMP)

Docetaxel Winthrop

(Docetaxel)

EMEA/H/C/000808/P46/0011

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

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

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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I. EXECUTIVE SUMMARY

This is an assessment of data for docetaxel, in accordance with the Article 46 of the regulation of the European Parliament and of the Council (EC) No.1901/2006, as amended, sanofi has submitted information on this international paediatric study EFC10339 completed on 29 may 2012. France is Rapporteur for this procedure.

On 16 May 2008, a Paediatric Investigation Plan (EMEA-000029-PIP01-07) has been adopted by the Paediatric Committee (PDCO) for docetaxel in nasopharyngeal carcinoma.

The objective of the agreed PIP EFC10339 study was to evaluate the efficacy and safety of the addition of docetaxel to the combination of cisplatin-5-fluorouracil (TCF) vs. Cisplatin-5-fluorouracil (CF) in the induction treatment of nasopharyngeal carcinoma (NPC) in children and adolescents.

II. RECOMMENDATION[1]

N/A

III. INTRODUCTION

On 14 august 2012, the MAH submitted a completed paediatric study for docetaxel, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A critical expert overview has also been provided.

The MAH states that, in accordance with Article 16(2) of Regulation (EC) No. 726/2004, the submitted data do not influence the benefit-risk balance for docetaxel and therefore do not require to take further regulatory action on the Marketing authorisation of Taxotere.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

Docetaxel is approved and marketed in the European Union in monotherapy or in combination for several indications in adults (breast cancer, locally advanced non-small cell lung cancer, metastatic gastric cancer, hormone refractory prostate cancer and head and neck cancer).
Docetaxel in Polysorbate 80 for intravenous administration is available in two presentations:

- Two-vials: 20 mg/0.5 ml and 80 mg/2 ml concentrate and solvent for solution for infusion
- One-vial: 20 mg/1 ml, 80 mg/4 ml and 160 mg/8 ml concentrate for solution for infusion

The docetaxel pharmaceutical formulation used in the EFC10339 study was the concentrate and solvent for solution for infusion.

[1] *The recommendation from section V can be copied in this section*

IV.2 Non-Clinical aspects

1. Introduction

N/A

2. Non-Clinical study (ies)

N/A

IV.3 Clinical aspects

1. Introduction

The MAH has submitted:

- The clinical study report of study ECF 10339:
- The EFC10339 abbreviated study report
- The pharmacokinetics results of docetaxel (when added to CF) in paediatric patients obtained from the EFC10339 study
- The clinical overview

The objective of the agreed PIP EFC10339 study was to evaluate the efficacy and safety of the addition of docetaxel to the combination of cisplatin and 5-fluorouracil (TCF) versus the cisplatin and 5-fluorouracil (CF) combination in the induction treatment of nasopharyngeal carcinoma (NPC) in children and adolescents.

The EFC10339 abbreviated study report presents the overall survival results from date of randomization to three years following the end of the consolidation period (ie, from study start date of 22 November 2007 to 23 February 2012 [last patient, last 3-year follow-up visit date]). In addition any new or updated serious adverse event information reported between 23 April 2009 and database lock on 29 May 2012, inclusive, is provided in updated and new patient narratives, as applicable.

The pharmacokinetics results of docetaxel (when added to CF) in paediatric patients obtained from the EFC10339 study, compared to those observed in adults after monotherapy at the same docetaxel dose (75 mg/m^2), have been analyzed in the BAY0016 study report.

2. Clinical study(ies)

As the EFC10339 study has been completed on 29 May 2012 (database lock for 3-year follow-up period), this paediatric study report is submitted under the Article 46 of the European Regulation (EC) 1901/2006, as amended.

Results taken from the agreed PIP EFC10339 study: a randomized, international, multicenter study in Paediatric patients comparing docetaxel + cisplatin + 5-fluorouracil (5-FU) (TCF) to cisplatin + 5-FU (CF) in the induction treatment of nasopharyngeal carcinoma (NPC) have been provided. This pivotal study enrolled 75 patients in a 2:1 randomization.

3. Discussion on clinical aspects

In study EFC10339, the overall complete response rate after induction treatment of NPC in children and adolescents showed that 1 patient out of 50 in the TCF group (2.0%) had an overall complete response while none of the 25 patients in the CF group had an overall complete response. Overall, there were no differences between the groups. The PR rate was 76% in the TCF group and 80% in the CF group. The distribution of OS rates over 3 years follow-up was similar in children and adolescents with NPC treated with docetaxel and CF compared with CF alone [Hazard ratio (95% CI): 0.67 (0.218-2.056), p=0.4809] and that docetaxel did not appear to increase the survival benefit in this patient population.

The response rates in study EFC10339 were lower than those assumed in the sample size calculations, which assumed a complete response rate of 31% after 3 cycles of induction therapy for the experimental arm (TCF) and a 20% complete response rate for the control arm (CF). The complete response rate assumption of 31% was based on a study by Rodriquez-Galindo et al in which Paediatric patients with NPC were treated with 4 courses of a regimen consisting of methotrexate (120 mg/m²) on Day 1, cisplatin (100 mg/m²) 24 hours later, and 5-FU (1000 mg/m²/day continuous infusion for 3 days with leucovorin 25 mg/m² every 6 hours for 6 doses. Radiation was given after chemotherapy. After 4 courses, a complete response rate of 31% was reported. The mean survival time was 23.45, and the mean overall survival was 60.13 months.

Mertens et al studied the treatment of NPC in paediatric patients in Europe. They administered 3 courses of preradiation chemotherapy consisting of methotrexate (120 mg/m²) on Day 1, cisplatin (100 mg/m²) on Day 1, and 5-FU (1000 mg/m² continuous infusion for 5 days with leucovorin 25 mg/m² every 6 hours for 6 doses beginning on Day 2. Radiation was given after chemotherapy. The complete response rate was 14% after 3 courses of preradiation chemotherapy.

In study EFC10339, the patients received only 3 courses of combination chemotherapy with TCF. The difference in response rate between EFC10339 and these 2 other older Paediatric studies may have been due to differences in response evaluation. In EFC10339, response was evaluated by a blinded panel of experts, which is a more reliable methodology than unblinded investigator evaluation. Mertens et al and Rodriguez-Galindo et al did not use independent blinded review, which may have contributed to higher reported response rates.

In addition, different response criteria were used in these studies. A CR in the Mertens study) was defined as disappearance of all target lesions on MRI. Responses were not independently confirmed. Rodriquez-Galindo et al defined CR as no evidence of disease by CT or MRI. In EFC10339, CR was defined as the complete disappearance of the target and non-target lesion(s) after radiological evaluation.

There are also differences in the extent of disease in these studies. Both the Mertens study and EFC10339 had higher proportions of patients with Stage 4 disease than did the Rodriquez-Galindo study. The proportion of patients with Stage 4 disease (53%) in the Mertens study was similar to that in EFC10339 (58.0% TCF, 52.0% CF). The proportion of patients with Stage 4 disease in the Rodriquez-Galindo study was only 13%, which may have contributed to the higher response rate.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Since the results presented in this clinical overview show that docetaxel monotherapy, as well as combination therapy with cisplatin and 5-FU was not demonstrated to be effective in treating

Nasopharyngeal carcinoma (based on the response rate during induction therapy), the MAH will not seek an indication for docetaxel therapy in paediatric patients.
This is considered acceptable.

- **Recommendation**

No further action required