Annex II

Scientific conclusions

Scientific conclusions

Epidemiological studies suggested an increased risk for ifosfamide-induced encephalopathy (IIE) with ifosfamide EG solution for infusion compared with ifosfamide powder for solution (Holoxan) (Hillaire-Buys, 2019; Chambord, 2019)[1,2]. The French national competent authority (ANSM) was of the view that the data available does not allow to rule out a possible similar increase for other solution formulations (i.e. solutions and concentrates for solutions).

On 28 February 2020 the ANSM therefore triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of ifosfamide-containing solutions and issue a recommendation as to whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.

The PRAC adopted a recommendation on 11 March 2021 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

The scope of this procedure is limited to solutions and concentrates for solutions, hereinafter commonly referred to as 'solutions'.

Overall summary of the scientific evaluation by the PRAC

Ifosfamide is a cytotoxic alkylating agent. Ifosfamide is a prodrug, converted to the active metabolite ifosfamide mustard in the liver by CYP450 hydroxylation. Ifosfamide-containing products are indicated as a single agent or in combination with other agents to treat a wide variety of malignancies in children and adults.

Ifosfamide-containing products are authorised in the EU as powder for reconstitution and as solution or concentrate for solution for infusion. The solution formulations are authorised in Germany (IFO-cell and IFO-cell N) and in France (Ifosfamide EG) only. Encephalopathy is a well-known adverse reaction of ifosfamide, and frequencies reported in the literature range between 10-30%.

When considering all the data submitted by the MAHs in relation to the risk of IIE with their products, including on quality and toxicology aspects, as well as data available in EudraVigilance, in the literature, and from earlier studies performed in France to investigate this matter, the PRAC was of the view that an increased risk of IIE with the solutions compared to the powder formulations could neither be confirmed nor excluded. Indeed, whilst several studies suggest an increased risk of IIE with the Ifosfamide EG compared to Holoxan, limitations to the datasets do not allow to exclude other possible reasons for those results. Further, a review of the quality of the medicinal products, could not identify differences that could explain the increased risk suggested in the epidemiological studies, nor relevant differences between the solutions in France and in Germany. In view of the inconclusive data, the PRAC considered that no specific advice could be provided to HCPs in this regard.

The PRAC noted that routine risk minimisation measures across the different product information were inconsistent. Taking into account all available information on CNS toxicity with this active substance, the PRAC considered that existing warnings should be revised as relevant to reflect the symptoms to look out for, the fact that this toxicity may become manifest within a few hours to a

[1] Chambord J, Henny F, Salleron J, et al. Ifosfamide-induced encephalopathy: Brand-name (Holoxan) vs generic formulation (Ifosfamide EG) J Clin Pharm Ther, 44 (2019), pp. 372-380

[2] Hillaire-Buys D, Mousset M, Allouchery M, et al. Liquid formulation of ifosfamide increased risk of encephalopathy: A case-control study in a paediatric population. Therapies, 2019 Oct 28

few days after administration. It should also be advised that if central nervous system (CNS) toxicity develops, administration of ifosfamide should be discontinued and whilst symptoms may persist for longer periods of time, in most cases it resolves within 48 to 72 hours of discontinuation. Nevertheless, occasionally, recovery has been incomplete and fatal cases have also been reported. It should be stated that CNS toxicity seems to be dose dependent. Risk factors should also be revised to reflect only those that have been confirmed in several independent studies: hypoalbuminaemia, impaired renal function, poor performance status, pelvic disease and previous or concomitant nephrotoxic treatments including cisplatin. No robust evidence supports an association with aprepitant, however healthcare professionals (HCP) should also be warned that due to the potential for additive effects, drugs acting on the CNS (such as antiemetics, sedatives, narcotics or antihistamines) must be used with particular caution or, if necessary, be discontinued in case of IIE. Finally, HCPs should be advised to closely monitor patients for symptoms of IIE and that methylene blue could be considered for the treatment and prophylaxis of ifosfamide-associated encephalopathies.

The PRAC considered whether additional pharmacovigilance activities would be useful to generate data allowing to elucidate this issue. However, in view of the overall size of the population exposed to ifosfamide and its heterogeneity, further studies are considered unlikely to generate data of sufficient robustness to definitely refute or confirm a differential risk.

It was noted however that out-of-specification (OOS) results were recorded in the worst-case studies (no sooner than 19 months from release and a day in diluted solution), the MAH is therefore required to perform in-use stability studies and submit the results to the relevant National Competent Authorities for assessment within the agreed timeframe. Updates to the product information should be proposed in accordance with the studies' results.

The PRAC concluded that the benefit-risk balance of ifosfamide solutions remains favourable, provided the agreed changes to the product information are implemented and provided the MAHs perform in-use stability studies and submit the results to the relevant National Competent Authorities for assessment within the agreed timeframe.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for ifosfamide-containing solutions (see Annex I).
- The PRAC reviewed the totality of the data provided by the marketing authorisation holders in writing and during an oral explanation in relation to the risk of ifosfamide-induced encephalopathy with their products, as well as data available in EudraVigilance, in the literature, and from studies performed in France to investigate this matter.
- Whilst some retrospective studies suggest an increased risk for encephalopathies in patients treated with ifosfamide-containing solutions compared to the powder formulation, the PRAC considers that such increased risk with the solution formulations could neither be confirmed nor excluded.
- The PRAC further considers that in order for the known risk of ifosfamide-induced encephalopathy to be appropriately minimised, existing warnings should be revised to take account of the latest available information with regards to the characteristics, associated risk factors and possible treatment, as well as the need for patients to be closely monitored.

- In view of the observed out-of-specification results in so-called worst-case studies, the PRAC recommends as a condition to the marketing authorisations that the MAH shall perform in-use stability studies and submit the results to the relevant National Competent Authorities for assessment within the agreed timeframe.

In view of the above, the Committee considers that the benefit-risk balance of ifosfamide-containing solutions remains favourable subject to the agreed condition to the marketing authorisations and taking into account the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for ifosfamide-containing solutions.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

The CMDh, as a consequence, considers that the benefit-risk balance of ifosfamide-containing solutions remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore, the CMDh recommends the variation to the terms of the marketing authorisations for ifosfamide-containing solutions.