ansm
Agence nationale de sécurité du médicament et des produits de santé

NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC

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This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by France (ANSM):

Product names in the referring member states	Ifosfamide EG
Active substances	Ifosfamide
Pharmaceutical forms	Solution for infusion, Concentrate for solution for infusion.
Strengths	All
Routes of Administration	All
Marketing Authorisation Holder(s) in the referring Member State	EG Labo

Background

Ifosfamide is an alkylating agent indicated in the treatment of various malignancies in oncology and haematology for children and adults. Ifosfamide is available either as a powder for solution for infusion or a solution for infusion or as a concentrate for solution for infusion. The dissolved powder and different solutions are administered directly or further diluted before administration.

In the EU, the solution forms of ifosfamide are only registered in France (Ifosfamide EG solution for infusion) and Germany (IFO-cell solution for infusion and concentrate for solution for infusion). In other Member States (MS), ifosfamide is only available as a powder form (Holoxan in France).

Encephalopathy is a well-known adverse reaction of ifosfamide and as such is addressed in sections 4.4 and 4.8 of the Summary of the Product Characteristics (SmPC) and related sections of the package leaflet.

Issues to be considered

In March 2015, a national pharmacovigilance survey was initiated in France following the observation of clusters of encephalopathy cases reported by paediatric oncology hospital departments. The objective of the survey was to review all cases of encephalopathy reported with ifosfamide collected by the French regional pharmacovigilance centres. In 2016, this investigation showed a higher incidence of spontaneous pharmacovigilance notifications of encephalopathy in children treated with Ifosfamide EG (solution for infusion) compared to Holoxan (powder for solution) by a factor of about 3 to 4.

At that time, it was hypothesized by the French medicines authority (Agence Nationale de Sécurité du Médicament et des produits de santé – ANSM) that the increased incidence of reported encephalopathy with Ifosfamide EG (solution for infusion) could be the consequence of increased levels of impurities in the solution for infusion and in particular a known neurotoxin. Indeed, ifosfamide is susceptible to hydrolytic degradation and accordingly, analytical results showed greater ifosfamide degradation in Ifosfamide EG (solution for infusion) than in Holoxan (powder for solution), with the overall content of impurities in the solution for infusion increasing markedly with storage, whilst only a limited increase over time was observed with the powder form.

Based on these results, and as a precautionary measure, the ANSM decided in June 2016 to temporarily reduce the shelf-life of Ifosfamide EG from 18 to 7 months (under refrigerated conditions

at 2-8°C); these changes were implemented in the SmPC of Ifosfamide EG. A study to measure the impact of this precautionary reduction of shelf-life was initiated at the same time. The results of this 2-years long pharmacovigilance case-control follow-up study in the paediatric population (2016-2018) were presented in 2019 to the ANSM (1) and showed a higher rate and higher odds for encephalopathy in children treated with Ifosfamide EG, compared with Holoxan powder for solution despite the reduced shelf-life (14.2% and 8.1%, respectively, OR = 1.87, 95% CI: 1.02 - 3.45, p = 0.04).

A retrospective study, using data from medical records of adult patients treated with ifosfamide EG or Holoxan in two medical centers in France from 2013 to 2017, with data analysed from medical records was also published (2). The frequency of ifosfamide-induced encephalopathy in the Holoxan group was 1.9% (2/103) against 10.2% (9/88) in the Ifosfamide EG group (P = 0.014)., A multivariate analysis showed that ifosfamide-induced encephalopathies occurred more often with Ifosfamide EG compared with Holoxan (OR = 7.4, 95% CI: 1.4-39.5, p = 0.0218).

In view of the observed higher risk of encephalopathy with Ifosfamide EG solution for infusion compared with Holoxan powder for solution, France triggered a European signal procedure in October 2019. In February 2020, the PRAC concluded that the two epidemiological studies evaluated within this signal procedure (1, 2) suggest an increased risk for ifosfamide-induced encephalopathy with ifosfamide EG solution for infusion compared with ifosfamide powder for solution (Holoxan). Whilst the PRAC acknowledged that uncertainties remain, the data raises serious concerns that need to be further addressed. Therefore, the PRAC considered that a thorough review at the EU level should be performed with the relevant expertise (e.g. quality, non-clinical experts, amongst others).
Based on the available data, France is of the view that it cannot be excluded that the risk applies to all solution formulations and especially in Germany which use solution for infusion (i.e. solution for infusion and concentrate for solution for infusion).

In view of the above and the necessity to take an action at EU level, France considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CMDh on the basis of a recommendation of the PRAC.

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Signed [redacted] Date 28 FEV. 2020

References:

1) HILLAIRE-BUYS, Dominique, MOUSSET, Mégane, ALLOUCHERY, Marion, et al. Liquid formulation of ifosfamide increased risk of encephalopathy: A case-control study in a pediatric population. Therapie, 2019 Oct

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2) J. Chambord, F. Henny, J. Salleron, B. Hombourger, P. Lider, J. Vigneron, et al. Ifosfamide-induced encephalopathy: Brand-name (Holoxan®) vs generic formulation (Ifosfamide EG®) J Clin Pharm Ther, 44 (2019), pp. 372-380