Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1495

Ifosfamide-containing solutions

Divergent statement

The following CMDh Member considers that the benefit-risk balance of ifosfamide-containing solutions is not favourable based on the following grounds:

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. In order to reduce this higher risk of encephalopathy, shelf life of the medicinal product IFOSFAMIDE EG was reduced from 18 to 7 months.

Following this measure, a case-control follow-up study (1) was conducted in France in the paediatric population. This study concluded on a higher risk of encephalopathy in children treated with Ifosfamide solution, compared with Ifosfamide powder (14.2% and 8.1%, respectively, OR = 1.87, 95% CI: 1.02 - 3.45, p = 0.04). A retrospective study (2) in adult patients treated with the powder or the solution formulation was also conducted based on data from medical records. The frequency of encephalopathy was higher in the Ifosfamide solution group, compared with the powder form (10.2% and 1.9%, p = 0.014).

In view of the observed higher risk of encephalopathy with the solution form compared to the powder one, France triggered a 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) which raised serious concerns that needed to be further addressed. Based on this conclusion, France triggered in February 2020 a referral under Article 31 of Directive 2001/83/EC, and asked 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 and CMDh concluded that an increased risk of encephalopathy with ifosfamide supplied as a solution could neither be confirmed nor excluded due to limitations in the data, and recommended an update of the existing warnings and further studies investigating the stability of the medicines. While the limitations of the available data and the recommended risk minimisation measures are noted, the referral could not exclude an increased risk nor completely elucidate its cause. It is therefore difficult to confirm whether the recommended risk minimisation measures will be effective. Furthermore, while the most likely cause of the increased risk of encephalopathy is related to the lack of stability of the liquid formulation and degradation products, there has been no recommendation to address the quality of the product before opening. Taking all these aspects into account, France considers that the benefit risk balance of the liquid form is negative, and that the powder form should be preferred. Indeed, as

ifosfamide is commonly available under its powder pharmaceutical form, the suggested increased risk with the solution formulation is not compensated by any benefit.

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 28

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

CMDh Member expressing a divergent opinion:

- Glenn Lastennet (FR)