11 March 2021
EMA/159195/2021
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

Invented name: Ifosfamide-containing solutions

INN/active substance: ifosfamide

Procedure number: EMEA/H/A-31/1495

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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Table of contents

1. Information on the procedure

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

2. Scientific discussion

2.1. Introduction

Ifosfamide is a cytotoxic alkylating agent. Ifosfamide is a prodrug, converted to the active metabolite ifosfamide mustard in the liver by CYP450 hydroxylation. Following its conversion, ifosfamide functions as an alkylating agent, interfering with DNA replication and transcription of RNA, and ultimately resulting in disruption of nucleic acid function.

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, including soft tissue sarcoma, osteosarcoma, non-Hodgkin lymphoma, ovarian cancer, small cell bronchial cancer, non-small cell bronchial cancer Hodgkin's lymphoma, testicular tumours, cervical cancer, metastatic breast cancer, ENT region cancer and acute lymphoblastic leukaemia.

These products available as powder for solution for injection, concentrate for solution for injection and solution for injection. In the European Economic Area (EEA), solutions are authorised in France (Ifosfamide EG) and in Germany (IFO-cell N), while concentrates for solution are only authorised in Germany (IFO-cell). The powder for solution formulation of ifosfamide is available in 16 Member States (MS) as well as the United Kingdom (Northern Ireland) (Holoxan and others).

The marketing authorisation holders (MAH) estimated patient exposure based on sales data between 1 January 2012 and 29 February 2020 to approximately 1,052 patient-years in France and approximately 920 patient-years for solution for infusion and 2,102 patient-years for the concentrate for infusion in Germany. These calculations are however limited by the wide variability in dosing of ifosfamide-containing products depending on indication, treatment regimens and patients characteristics including age.

[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

Encephalopathy is a well-known adverse reaction of ifosfamide, and frequencies reported in the literature range between 10-30% (Lo, 2016; David, 2005; Pelgrims, 2000)[3,4,5].

Following the introduction of the solution formulation in France clusters of encephalopathy cases were reported by oncopaediatric oncology hospital departments. A survey was thus initiated to review all reports collected by the French regional pharmacovigilance centres of cases of encephalopathy with ifosfamide and found a higher incidence in children treated with the solution compared to the powder formulation, by a factor of 3 to 4. As a precautionary measure, following the assumption that this difference may be due to impurities increasing progressively in solution, the ANSM decided in June 2016 to temporarily reduce the shelf-life of the solution formulation from 18 to 7 months. A follow-up case-control study performed over 2016-2018 still found a higher rate and higher odds for encephalopathy in children treated with the solution, compared with the powder (Hillaire-Buys, 2019)[2]. In parallel, a retrospective study, using data from medical records of adult patients treated with either formulations in France between 2013 and 2017, also found that ifosfamide-induced encephalopathies occurred more often with the solution than with the powder formulation (Chambord, 2019)[1]. Both latest epidemiological studies were then assessed in a signal procedure and PRAC concluded that a thorough review at the European Union (EU) level should be performed as whilst uncertainties remained, the data raised serious concerns that needed to be further addressed. The ANSM then initiated this referral procedure.

The PRAC considered all available data, including studies performed in France investigating this matter and that submitted by the MAH on the quality and toxicology of its product and safety data on the risk of encephalopathy, as well as data from EudraVigilance. A summary of the most relevant information is included below.

The benefit of ifosfamide-containing products is well established and does not differ with the formulation. No significant elements have been submitted within this procedure that would question the efficacy.

2.2. Data on safety

2.2.1. Characteristics of ifosfamide-induced encephalopathy

The symptoms of encephalopathy may include the following: confusion, somnolence, coma, hallucination, blurred vision, psychotic behaviour, extrapyramidal symptoms, urinary incontinence and seizures. IIE are generally reversible, however, occasionally, recovery has been incomplete and fatal outcomes have been reported (Séjourné, 2014; Shin, 2011)[6,7].

The suspected causes of IIE are the metabolites chloroacetaldehyde and chloroethylamine. After administration, up to 50% of ifosfamide is deactivated by the removal of chloroethyl. During this step chloroacetaldehyde is formed. Chloroethylamine is a degradation product of the active metabolite ifosfamide mustard. Chloroethylamine is further metabolised to chloroacetaldehyde, but it is also neurotoxic in itself.

[3] Lo Y, Shen LJ, Chen WH, Dong YH, Wu FL. Risk factors of ifosfamide-related encephalopathy in adult patients with cancer: A retrospective analysis. J Formos Med Assoc. 2016;115(9):744-751.
[4] David KA, Picus J. Evaluating risk factors for the development of ifosfamide encephalopathy. Am J Clin Oncol. 2005;28(3): 277–280
[5] Pelgrims J, De Vos F, Van den Brande J, et al. Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. Br J Cancer. 2000;82:291–294.
[6] Séjourné A, Noal S, Boone M, Bihan C, Sassier M, Andrejak M, Chauffert B. Two cases of fatal encephalopathy related to Ifosfamide: an adverse role of aprepitant? Case Rep Oncol. 2014 Sep 25;7(3):669-72.
[7] Shin YJ, Kim JY, Moon JW, You RM, Park JY, Nam JH. Fatal Ifosfamide-induced metabolic encephalopathy in patients with recurrent epithelial ovarian cancer: report of two cases. Cancer Res Treat. 2011;43(4):260-263.

2.2.1.1. Time-to-onset and recovery

In a study in 88 patients, out of which 7 (8%) developed encephalopathy, the median time until IIE onset was 74 h (range 56-115h) after the initiation of ifosfamide and the median time to recovery was 57.5 h (range 17-129h) (Ide, 2019)[8]. In the 11 cases reported by Chambord and colleagues, symptoms developed in less that 24h for 3 patients and between 24-48h for 9 patients (Chambord, 2019)[1]. In an analysis of reports of encephalopathy between 2004 and 2018 from the US Food and Drug Administration Adverse Event Reporting System (FAERS) and the Japanese Adverse Drug Event Report (JADER) databases the median duration (interquartile range) for IIE was 3.0 (2.0–5.0) days for encephalopathy (PT) (94.1% occurring within the first 7 days of administration) and 3.0 (1.0–5.0) days for encephalopathy standard medical dictionary for regulatory activities (MedDRA) query (SMQ) (87.7% occurring within the first 7 days of administration) (Shimada, 2019)[9]. In the 8 patients (18%) who developed neurotoxicity in the study by Howell and colleagues, the median duration of ifosfamide-induced neurotoxicity was 19.5 hours (3–78 hours) for patients treated with 3.75 g/m2/day for two days and 23 hours (22.5–55 hours) for patients treated with 2.5 g/m2/day for four days (Howell, 2008)[10]. The mean time to resolution was also reported to be 2.58 (interquartile range 1–3) days among 20 patients cycles with IIE in another retrospective study (Modi, 2020)[11]. In a retrospective study of 186 cases in France between 2012 and 2015 (see also 2.2.2.3.1.), the time of onset was within 6 hours after the end of the infusion for both formulations in almost half the cases and rarely exceeded 24 hours. Almost all patients recovered (93.5%, n=174), albeit not fully for 3 patients, while 3 patients had not yet recovered and 8 fatal cases were reported, including 6 possibly related to the central nervous system (CNS) toxicity event, information was not available for the last 2 patients.

In the Hillaire-Buys study, altogether 53% of cases occurred in the first treatment course, 33% between courses 2 and 4 and 14% between courses 5 and 9 (Hillaire-Buys, 2019)[2].

Recurrence of encephalopathy in subsequent cycles was reported in several studies, including up to around 50% (Sweiss, 2008; Rieger, 2004; Filhon, 2016; Modi, 2020)[12,13,14,11].

Overall, it is considered that an ifosfamide induced CNS toxicity may become manifest within a few hours to a few days after administration and not necessarily only after the first administration. If CNS toxicity develops, administration of ifosfamide should be discontinued. Whilst symptoms may persist for longer periods of time, in most cases IIE resolves within 48 to 72 hours of ifosfamide discontinuation.

2.2.1.2. Risk factors for ifosfamide-induced encephalopathy

Many risk factors for the development of encephalopathy have been discussed in the literature. However, no consensus has been attained so far on the importance and significance of each of these factors. The analysis of risk factors is limited as most studies include only very few patients. In

[8] Ide Y, Yanagisawa R, Kubota N, et al. Analysis of the clinical characteristics of paediatric patients who experience ifosfamide-induced encephalopathy. Pediatr Blood Cancer. 2019;66(12):e27996.
[9] Shimada K, Hasegawa S, Nakao S, et al. Adverse event profiles of ifosfamide-induced encephalopathy analysed using the Food and Drug Administration Adverse Event Reporting System and the Japanese Adverse Drug Event Report databases. Cancer Chemother Pharmacol. 2019 Nov;84(5):1097-1105.
[10] Howell JE, Szabatura AH, Hatfield Seung A, Nesbit SA. Characterization of the occurrence of ifosfamide-induced neurotoxicity with concomitant aprepitant. J Oncol Pharm Pract. 2008;14(3):157-162.
[11] Modi JN, Cimino SK. Incidence of ifosfamide induced encephalopathy in patients receiving concomitant fosaprepitant. J Oncol Pharm Pract. 2020 Nov 8:1078155220971794.
[12] Sweiss KI, Beri R, Shord SS. Encephalopathy after high-dose Ifosfamide: a retrospective cohort study and review of the literature. Drug Saf. 2008;31(11):989-996
[13] Rieger C, Fiegl M, Tischer J, Ostermann H, Schiel X. Incidence and severity of ifosfamide-induced encephalopathy. Anticancer Drugs. 2004;15(4):347-350.
[14] Filhon B, Lacarra B, Hervouet C, Jaffray M, Schneider P, Vannier JP. Ifosfamide-induced encephalopathy due to a novel formulation of ifosfamide. Pediatr Blood Cancer. 2016;63(2):372-373.

addition, many potential risk factors have only been observed in one study, in case series or single case reports.

Risk factors for IIE are inconsistently mentioned across the PI of ifosfamide solutions and concentrates for solutions, taken jointly the following are mentioned: higher dose, rapid intravenous administration, elevated serum creatinine, hepatic dysfunction, low bilirubin, low haemoglobin levels, decreased white blood count, acidoses, low serum bicarbonate, electrolyte imbalance, hyponatraemia and inappropriate ADH (vasopressin) secretion, water intoxication, low fluid intake, presence of brain metastases, prior CNS disease, brain irradiation, cerebral sclerosis, peripheral vasculopathy, presence of tumour in lower abdomen, bulky abdominal disease, poor performance status in elderly or younger patients, obesity, female gender, individual predisposition, interaction with other medicines (e.g. aprepitant, CYP 3A4 inhibitors, phenobarbital), alcohol, drug abuse.

2.2.1.2.1. Dose and method of administration

As mentioned above, the risk of IIE is mentioned in some of the PI as seemingly increasing with the dose. Indeed, in a retrospectively study in 61 Japanese patients with bone and soft tissue sarcomas, ifosfamide doses ≥9 g/m² have been identified as risk factor for severe encephalopathy (Tajino, 2010)[15]. The retrospective study of reports of encephalopathy from the FAERS and the JADER databases (including over 500 cases reporting the preferred term (PT) encephalopathy), found that statistically significantly higher average doses had been administered to patients with encephalopathy compared to those without encephalopathy (2022.8 ± 592.8 (mean ± standard deviation) vs. 1568.5 ± 703.2 mg/m^2, respectively ($p < 0.05$)) (Shimada, 2019)[9]. In a study of the toxicity and efficacy of oral ifosfamide in 64 patients, the number of patients experiencing CNS toxicity increased with the dose (Manegold, 1992)[16]. A significant association between IIE risk and higher daily dose was also identified in a retrospective cohort study in 200 adults of whom 29 experienced encephalopathy (f 1824 ± 706.6 mg/m2 vs. 1912.1±399.8 mg/m2; p=0.009) (Szabatura, 2015)[17]. No difference in daily dose (2329.0 ± 1073.1 mg/m2 vs. 2331.1 ±1039.2 mg/m2; p=0.891) or in the dose per cycle (5603.4 ± 1949.4 vs. 5596.8 ± 1910.8; p=0.859) was however reported in a chart review of 337 patients, including 38 (11%) patients with IIE (Lo, 2016)[3]. Unlike other risk factors, there is no common definition of 'high dose' and levels reported across studies differ with the patient population included, thus limiting comparability. In addition, the variability of treatment regimens and doses given limits the detection of differences in small study populations, thus results from Shiamada and colleagues are considered more relevant to analyse a dose effect. Further, it is noted that whilst no differences in the median dose have been observed in the study by Lo and colleagues, patients treated with daily dosages of <2 mg/m²/day developed less encephalopathies (7/101; 6.9%) than patients receiving higher doses (31/236, 13.1%). Moreover, from a biological perspective, it is considered plausible that a higher dose is associated with a higher risk.

Duration of infusion is also inconsistently mentioned as a risk factor in the product information (PI). This is in line with available literature data as the evidence that infusion duration could be a potential risk factor for encephalopathy development is inconclusive (Cerny, 1990; Boddy, 1995; Kaijser, 1996; Silies, 1997; Singer, 1998; Kerbusch, 2001; David, 2005; Sweiss, 2008; Chambord

[15] Tajino T, Kikuchi S, Yamada H, Takeda A, Konno S. Ifosfamide encephalopathy associated with chemotherapy for musculoskeletal sarcomas: incidence, severity, and risk factors. J Orthop Sci. 2010 Jan;15(1):104-11.
[16] Manegold C, Bischoff H, Fischer JR, et al. Oral ifosfamide-mesna: A clinical investigation in advanced non-small-cell lung cancer. Annals of Oncology, Volume 3, Issue 9 : 723-726, 1992.
[17] Szabatura AH, Cirrone F, Harris C, et al. An assessment of risk factors associated with ifosfamide-induced encephalopathy in a large academic cancer center. J Oncol Pharm Pract. 2015;21(3):188-193.

2019)[18,19,20,21,22,23,24,12,1]. Indeed, whilst an autoinduction effect was observed in a few small studies the difference between short and long duration of infusion was considered to be of minor clinical importance as it was comparable with the interindividual variability (22%) (Kerbusch, 2001)[23]. Furthermore, in a recent retrospective study in 191 adult patients longer infusion was identified as a potential risk factor for encephalopathy (Chambord, 2019)[1]. This could not be confirmed due to study limitations (please refer to 2.2.2.2.2.).

Therefore, whilst the CNS toxicity seem indeed to be dose dependant, the speed of intravenous administration is not considered to be a confirmed risk factor.

2.2.1.2.2. Patient-associated risk factors

Among the studies investigating risk factors, one of the biggest study population was analysed in a retrospective cohort study including 237 adult patients treated with ifosfamide, of whom 38 developed an encephalopathy (David, 2005)[4]. The only significant risk factor for the development of encephalopathy within this study was hypoalbuminaemia. Low albumin levels have also been identified as risk factor in a retrospective study of 45 inpatients with Sarcoma (Howell, 2008)[10], in the above mentioned studies by Szabatura and colleagues (OR: 0.148; 95%CI [0.05-0.44]; p = 0.001) (Szabatura, 2015)[17], and by Lo and colleagues (Lo, 2016)[3]. In a further retrospective study, of 51 patients who received 215 total cycles of ifosfamide, IIE was documented in twenty (9.3%) patient cycles, out of which 7 (35%) had low albumin level, whereas low albumin levels were reported in 10 (5.1%) cycles without IIE (p < 0.001) (Modi, 2020)[11]. A literature review of articles published between 2008 and 2018 also identified hypoalbuminemia as a risk factor (Lee Brink, 2020)[25].

An explanation for this effect could be that decreased albumin levels lead to an increase in the plasma concentration of ifosfamide and allow for increased conversion into neurotoxic metabolites that freely cross the blood–brain barrier.

Sarcoma diagnosis was also identified as a risk factor in the study by Szabatura, where 24/100 of the sarcoma patients developed IIE and only 5/100 of the lymphoma patients (OR: 7.79; 95%CI [2.43-25.01]; p=0.001). In the cohort study by David and colleagues the diagnosis was not analysed as a risk factor, but 20% of the patient with sarcoma diagnosis developed IIE in comparison to 12% of the lymphoma patients. Diagnosis of sarcoma was also identified in the study by Hillaire-Buys and colleagues as a significant risk factor for the development of encephalopathy, however a confounding by dose might be possible as over half of the sarcoma patients received high doses (Hillaire-Buys, 2019)[2]. Importantly, in the study by Szabatura and colleagues, among the patients with sarcoma, encephalopathy occurred most often in patients with disease in the pelvis and retroperitoneum. Meanwell and colleagues, further to a study in 77 patients with advanced malignancies (out of which 7 experienced encephalopathy), also found that among the sarcoma

[18] Cerny T, Castiglione M, Brunner K, et al. Ifosfamide by continuous infusion to prevent encephalopathy [letter]. Lancet 1990.
[19] Boddy AV, Yule SM, Wyllie R, Price L, Pearson ADJ and Idle JR (1995) Comparison of continuous infusion and bolus administration of ifosfamide in children. Eur J Cancer 31:785–790.
[20] Kaijser GP, Keizer HJ, Beijnen JH, Bult A, Underberg WJ. Pharmacokinetics of ifosfamide, 2- and 3-dechloroethylifosfamide in plasma and urine of cancer patients treated with a 10-day continuous infusion of ifosfamide. Anticancer Res. 1996;16(5B):3247-3257.
[21] Silies H., Boos J., Blaschke G., Jürgens H. (1997) Infusion rate does not influence ifosfamide side-chain metabolism. In: Büchner T., et. Al. (eds) Acute Leukemias VI. Haematology and Blood Transfusion / Hämatologie und Bluttransfusion, vol 38. Springer, Berlin, Heidelberg.
[22] Singer JM, Hartley JM, Brennan C, Nicholson PW and Souhami RL (1998) The pharmacokinetics and metabolism of ifosfamide during bolus and infusional administration: a randomized cross-over study. Br J Cancer 77:978–984.
[23] Kerbusch T et al. Influence of dose and infusion duration on pharmacokinetics of ifosfamide and metabolites. Drug Metab Dispos. 29(7): 967-75 (2001).
[24] David KA, Picus J. Evaluating risk factors for the development of ifosfamide encephalopathy. Am J Clin Oncol. 2005;28(3): 277–280.
[25] Lee Brink A, Bowe C, Dains JE. Risk Factors for Ifosfamide-Related Encephalopathy in Adult Cancer Patients: An Integrative Review. J Adv Pract Oncol. 2020;11(4):368-380.

patients, patients with pelvic disease were more prone to develop IIE (Meanwell, 1986)[26]. Further, decreased renal function and platin exposure have also been identified as risk factors in the above-mentioned studies by Ide and colleagues (Ide, 2019)[8], by Szabatura (previous Cisplatin exposure OR: 12.47; 95%CI [1.97-79.09]; p= 0.007) and in a study in 97 children and adolescents, out of which 22 developed neurotoxicity (Pratt, 1990)[27]. Other nephrotoxic agents were also identified to contribute to IIE (Ide, 2019)[8]. This is further supported by the above-mentioned literature review which also identified of impaired renal function as a risk factor (Lee Brink, 2020)[25].

The postulated common pathomechanism behind those risk factors, is that renal dysfunction may precipitate encephalopathy by reducing the clearance of ifosfamide and its metabolites. Whereas pelvic disease in sarcoma patients may obstruct renal blood flow and subsequently the filtration rate, thus also leading to a higher risk of encephalopathy. Likewise, previous cisplatin exposure is associated with a decreased renal function (Richards, 2010; Ide, 2019; Szabatura, 2015)[28,8,17].

The study by Lo and colleagues further identified Eastern Cooperative Oncology Group (ECOG) performance status greater than or equal to 2 as a risk factor (adjusted OR: 5.15; 95%CI [2.35-11.28]) for the development of encephalopathies (Lo, 2016)[3]. This risk factor is further supported by the results of a retrospective study in 187 patients, out of which 8 experienced IIE (OR: 9.52; 95%CI [2.38-38.80]) (Stern, 2017)[29].

Finally, the most discussed possible risk factor is concomitant use of aprepitant. Several case reports and case series discussed aprepitant as possible risk factors, but the risk was never confirmed in studies. In a review of 5 case reports and 6 retrospective studies, all case reports attributed ifosfamide-induced neurotoxicity to an aprepitant-ifosfamide drug interaction, but none of the 6 retrospective studies evaluating this possible interaction demonstrate a statistically significant difference in ifosfamide-induced neurotoxicity rates in the presence of aprepitant (Patel, 2017)[30]. Nevertheless, as the potential for additive effects on the CNS cannot be ruled out, it is considered that medicinal products 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.

Other risk factors discussed in the literature, have either only been identified in single studies or case series, or conflicting results were reported.

In conclusion, the best documented risk factors are hypoalbuminaemia, decreased renal function, poor performance status, pelvic disease and previous or concomitant nephrotoxic treatments including cisplatin.

2.2.1.2.3. Paediatric patients

The frequency of encephalopathy in paediatric patients seems to be comparable to that in adult patients. Studies reported an incidence of 8%-23% per paediatric patients and 14%-19% per treatment course (Ide, 2019; Pratt, 1986; Pratt, 1990)[8,31,27]. No comparative study investigating

[26] Meanwell CA, Blake AE, Kelly KA, Honigsberger L, Blackledge G. Prediction of ifosfamide/mesna associated encephalopathy. Eur J Cancer Clin Oncol 1986;22:815–819
[27] Pratt CB, Goren MP, Meyer WH, Singh B, Dodge RK. Ifosfamide neurotoxicity is related to previous cisplatin treatment for paediatric solid tumours. J Clin Oncol. 1990;8(8):1399-1401.
[28] Richards, A., Marshall, H., & McQuary, A. (2010). Evaluation of methylene blue, thiamine, and/or albumin in the prevention of ifosfamide-related neurotoxicity. Journal of Oncology Pharmacy Practice, 17(4), 372–380.
[29] Stern N, Sakji I, Defachelles AS, et al. Incidence et facteurs de risque de l'encéphalopathie à l'ifosfamide chez les patients suivis pour un sarcome [Incidence and risk factors for ifosfamide-related encephalopathy in sarcoma patients]. Bull Cancer. 2017 Mar;104(3):208-212. French.
[30] Patel P, Leeder JS, Piquette-Miller M, Dupuis LL. Aprepitant and fosaprepitant drug interactions: a systematic review. Br J Clin Pharmacol. 2017;83(10):2148-2162.
[31] Pratt, C. B. Central nervous system toxicity following the treatment of paediatric patients with ifosfamide/ mesna. J. Clin. Oncol., 4: 1253-1261, 1986

differences between adults and paediatric patients is available and, overall, data on risk factors in the paediatric population is very limited.

The pharmacokinetic and the metabolism of ifosfamide in children was analysed in a few studies which observed differences in the relative rates of side-chain dechlorethylation, indicating an inter-individual variability in the formation of chloroacetaldehyde (Boddy, 1993; Kerbusch, 2001)[32,23]. This variability has also been observed in a further publication which described increased chloroacetaldehyde serum concentrations in two paediatric patients with encephalopathy in comparison to four asymptomatic paediatric patients (Goren, 1986)[33]. As in adult patients autoinduction of ifosfamide metabolism following continuous or repeated exposure has been observed in paediatric patients and is considered of minor clinical relevance (Kaijser, 1998)[34]. Therefore, results in children and adults suggest that the interindividual variability is greater than variability due to age.

In conclusion, the metabolism of ifosfamide and risk factors for encephalopathy seem to be comparable in children and adults and has a wide inter-individual variability in all age groups.

2.2.1.3. Use of methylene blue

The PI of those products make reference to methylene blue as a possible treatment for encephalopathy in sections 4.4 and 4.9, acknowledging that available data do not allow to confirm its efficacy. The use of methylene blue as a prophylactic agent was initially based on abnormal amounts of glutaric acid and sarcosine identified in the urine during IIE (Küpfer 1994)[35]. A relationship between glutaric aciduria and 2-chloroethylamine, but not other ifosfamide metabolites, has been identified in rats. Several hypotheses have been proposed, but methylene blue's mechanism of action is currently unknown (Küpfer, 1994; Bernard, 2010; Séjourné, 2014)[35,36,6].

In a study in 9 patients, no encephalopathy occurred while the patients were given methylene blue, while the 3 patients who did not continue methylene blue all had an IIE (Aelischmann, 1998)[37]. Similar results were reported by Pelgrims and colleagues who concluded, based on different methylene blue protocols used in 12 patients, that it was an effective treatment for IIE and suggested that it may also be used as a prophylactic agent (Pelgrims, 2000)[5]. Available data from case reports also indicate that methylene blue is an option in the treatment of IIE, especially in patients with severe symptoms of toxicity (Patel, 2006)[38]. In a retrospective study of 186 cases in France between 2012 and 2015 (see also 2.2.2.3.1.), methylene blue was used with curative intent in around 60% of cases (n=112) and was deemed to be efficacious in all but 5 cases. It was further used to prevent recurrence in 46 patients, out of which 12 experienced another event. In the study by Hillaire-Buys, out of the 18 patients administered methylene blue as prophylaxis recurrence occurred in two cases (11%), whilst no recurrence was noted in 16 cases (89%).

On the other hand, in a retrospective cohort study 5 patients were administered prophylactic methylene blue before a second cycle of high dose ifosfamide and all developed encephalopathy

[32] Boddy V et al. Pharmacokinetics and metabolism of ifosfamide administered as a continuous infusion in children. Cancer Res. 1993; 53: 3758-3764.
[33] Goren MP, Wright RK, Pratt CB, Pell FE. Dechloroethylation of ifosfamide and neurotoxicity. Lancet. 1986 Nov 22;2(8517):1219-20.
[34] Kaijser, G & Kraker, J & Bult, A & Underberg, W.J.M. & Beijnen, J. (1998). Pharmacokinetics of ifosfamide and some metabolites in children. Anticancer research. 18. 1941-9.
[35] Küpfer A, Aeschlimann C, Wermuth B, Cerny T. Prophylaxis and reversal of ifosfamide encephalopathy with methylene blue. Lancet 1994; 343: 763-4.
[36] Bernard PA, McCabe T, Bayliff S, Hayes D Jr. Successful treatment of ifosfamide neurotoxicity with dexmedetomidine. J Oncol Pharm Pract. 2010;16(4):262-265.
[37] Aeschlimann C, Kupfer A, Schefer H, Cerny T: Comparative pharmacokinetics of oral and intravenous ifosfamide/mesna/methylene blue therapy. Drug Metab Dispos 1998;26:883–890.
[38] Patel PN. Methylene blue for management of Ifosfamide-induced encephalopathy. Ann Pharmacother. 2006 Feb;40(2):299-303.

(Sweiss, 2008)[12]. The authors also mentioned that other publications have found that methylene blue does not prevent IIE.

Considering this conflicting and limited data and that encephalopathy is also known to resolve spontaneously, in the absence of data from controlled clinical trials, the usefulness of methylene blue remains unclear but it may be considered for the treatment and prophylaxis of ifosfamide-associated encephalopathies.

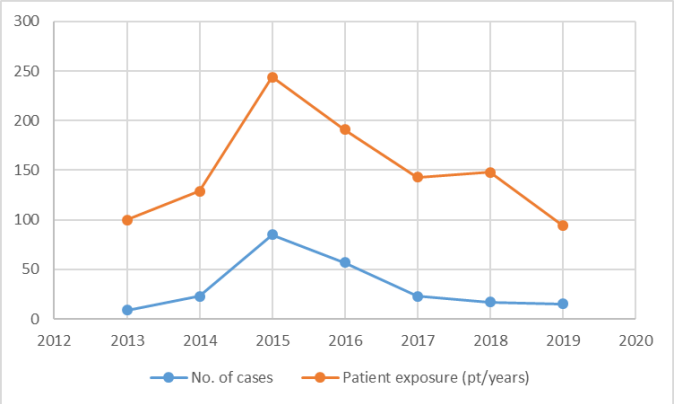
2.2.2. Safety data on the possible excess risk of IIE with solutions

2.2.2.1. Data from EudraVigilance

The EudraVigilance (EV) database was searched using the PT encephalopathy and ifosfamide-containing products as suspected product, regardless of the formulation, for the period between 1 January 2012 to 6 April 2020. A total of 577 cases were retrieved. Fifty-two percent (52%) of cases concerned female patients, 44% male patients and the gender was not reported in the remaining cases. In 45 cases the outcome was fatal, of these, 24 patients received ifosfamide powder, 3 ifosfamide solution, and the pharmaceutical form was not reported in the remaining 18 cases.

Of the afore mentioned 577 cases, 434 were reported in the EEA. Of these cases, 393 occurred in France and 11 in Germany. Specifically, for the solution formulations, 229 cases were reported in France and 1 in Germany. Out of the 229 cases reported in France for solution formulations, 102 occurred in children. The number of cases reported in patients receiving ifosfamide solution in France appeared correlated with patient exposure in a non-proportional fashion (see below figure). A peak in reporting is observed in France in 2015, the year following the initiation of the national investigation.

Figure 1. Evolution of the number of cases reported for ifosfamide solutions in France vs. exposure in patient-years



It should be noted that since 2014, the solution formulation has been the subject of a national pharmacovigilance investigation in France to compare the incidence of encephalopathies in the paediatric population between the two formulations. The significant increase in the number of cases was noted in the year after when a survey was also performed requesting from French pharmacovigilance centres information on ifosfamide consumption by type of formulation and occurrence of encephalopathies. In June 2016, the shelf-life was reduced in France from 18 to 7 months as a precautionary measure. Therefore, reporting bias due to the increased awareness cannot be excluded. The number of reports decreased with the exposure, and in 2018 and 2019 the number of cases reporting IIE with liquid form was even lower than with powder formulation (17 vs. 18 and 15 vs. 18, respectively in 2018 and 2019).

The different reporting rates in Germany and France partly reflects the systematic evaluation of patient records in France to identify cases of encephalopathy in the recent years and the awareness among HCPs of a possible increased risk for encephalopathies with the liquid formulation.

No definite conclusion can be made based on this data considering the limited information available on indication, medical history or concomitant medication.

2.2.2.2. Data from the literature

No data from prospective clinical trials comparing the risk of encephalopathies of different ifosfamide-containing products is available.

2.2.2.2.1. Hillaire-Buys 2019 study

A multi-centric case control study was carried out in 25 in paediatric oncology departments of university hospitals in France between July 2016 and July 2018 (Hillaire-Buys, 2019)[2]. All children receiving liquid formulation or lyophilised powder formulation of ifosfamide were included. Data was collected from medical records. The diagnosis of encephalopathy was defined as: "neurological and psychiatric symptoms, electroencephalogram (EEG) results if available" and grading was performed according to "common toxicity criteria (CTC) graduation for neurotoxicity (5th version) by two different CRPV [regional pharmacovigilance centre] senior members blinded to the exposure".

A logistic regression was performed, adjusted for age, gender, and indication of sarcoma. In order to gain 80% power at a bilateral type I error (α) of 5%, 81 cases are necessary to show a two-fold elevated "risk of encephalopathy" (OR = 2) with two controls per case under the assumption of 30% controls being exposed to the liquid formulation.

Of the 420 patients treated with Holoxan 34 developed an encephalopathy and of the 127 patients treated with Ifosfamide EG 18 reported an encephalopathy. The authors found an excess-risk of encephalopathy associated with ifosfamide 7-month shelf-life liquid formulation compared to lyophilised powder (adjusted OR: 1.91, 95%CI [1.03-3.53]).

It is noted that no operational definition of encephalopathy is provided and the applied criteria for the diagnosis of encephalopathy can vary between the cases and the validity of the diagnosis cannot be verified.

In general, confounding by indication is expected to be low as both products contain the same active substance and have the same indication. Despite this, differences in diagnosis and treatment protocols are noted between patients of each treatment arm developing encephalopathies (see below table). This could indicate imbalances in known risk factors for encephalopathy (e.g. dose of ifosfamide, concomitant medications, concomitant disease). Indeed, the total dose of ifosfamide per cycle and the concomitant cytotoxic medication differ per treatment protocol. The proportion of cases receiving a cumulative dose of ≥ 30 g/m2 in the Ifosfamide EG case group (6/26) exceeded the corresponding proportion in the Holoxan case group (6/14) by approximately 20%. No information on the daily dose or dose per cycle was provided. However, as the cycle of onset is comparable between both groups, the difference in cumulative dose indicates a difference in dose per cycle, which could therefore indicate a dose effect.

A higher rate of sarcoma diagnosis has been reported for patients who developed encephalopathy treated with Ifosfamide EG (88.9% vs. 73.5%). The difference is not significant, due to the low number of patients. More patients were also treated with EURO-Ewing in the Ifosfamide EG group, whereas 25% of the Ewing sarcomas are located in the pelvic area (Szabatura, 2015)[17]. An increased occurrence of encephalopathy has been observed in sarcoma patients with pelvic disease (see also

2.2.1.2.2.). Nonetheless, data adjustment by age, gender and indication (sarcoma) had only a negligible effect on the estimate and supports that confounding by indication may be low (crude OR: 1.87; 95%CI [1.02-3.45]).

Table 1. Sarcoma indication and treatment protocols in patient with encephalopathy

	Total cases (n = 52)	Cases exposed to Holoxan® (n = 34)	Cases exposed to Ifosfamide EG® (n = 18)
Indication for sarcoma, % (n)			
Yes	78.8 (41)	73.5 (25)	88.9 (16)
No	21.2 (11)	26.5 (9)	11.1 (2)
Treatment protocol, % (n)			
OS2006	42.3 (22)	44.1 (15)	44.4 (8)
EURO-EWING	19.2 (10)	8.8 (3)	33.3 (6)
RMS 2005	9.62 (5)	11.8 (4)	5.5 (1)
EPSSG-NRSTS	7.7 (4)	8.8 (3)	5.5 (1)
Total sarcoma regimens	78.8 (41)	73.5 (25)	88.9 (16)
ATRT09	3.8 (2)	2.9 (1)	5.5 (1)
EsPhaLL	1.9 (1)	2.9 (1)	0 (0)
SPARKLE	1.9 (1)	5.9 (2)	0 (0)
TGM 2013	1.9 (1)	0 (0)	5.5 (1)
SIOP	5.8 (3)	8.8 (3)	0 (0)
P6 Kushner	1.9 (1)	2.9 (1)	0 (0)
Other	1.9 (1)	2.9 (1)	0 (0)
Cumulative IFO dose received before encephalopathy (extrapolated from protocol), % (n)			
$< 10\,g/m^2$	40.0 (16)	46.2 (12)	28.6 (4)
$10 < D \leq 30\,g/m^2$	30.0 (12)	30.8 (8)	28.6 (4)
$30 < D \leq 50\,g/m^2$	15.0 (6)	11.5 (3)	21.4 (3)
$> 50\,g/m^2$	15.0 (6)	11.5 (3)	21.4 (3)
Unknown	12	8	4

The controls have not been analysed for possible differences between the Holoxan cohort and the Ifosfamide EG cohort, hence it is not known whether the differences between the cases reflect differences between the complete cohorts of patients. As with all observational studies, residual confounding, due to factors that were not considered, cannot be excluded. In particular, other known risk factors were not considered in this study, such as previous treatment with cisplatin or hypoalbuminemia were not recorded in this study. Of note however, no significant imbalance in renal function was noted.

A confounding by differences between the two treatment cohorts cannot be excluded.

In conclusion, in light of the limitations highlighted a bias cannot be excluded and considering the low precision of the risk estimate, the study is not considered sufficient to conclude on an increased risk for encephalopathies in patients treated with Ifosfamide EG.

2.2.2.2.2. Chambord 2019 study

A retrospective study compared the occurrence of IIE according to the formulation used in 191 adults from two clinical centres from 2013 to 2017 (Chambord, 2019)[1]. The frequency of IIE in the Holoxan group was 1.9% (2/103) against 10.2% (9/88) in the Ifosfamide EG group (p = 0.014). The low reporting rate of IIE in the Holoxan group (1.9%) is of note. Most literature reports report a frequency of 10% or higher.

Selection criteria has not been described and it is not clear why only the first formulation received was considered for patient who received both formulations. Although the role of the infusion time and the use of aprepitant in the development of IIE is still unclear, it was noted that the median infusion time was significantly longer in the Holoxan group (12 vs 3 hours, p < 0,001) and administration of aprepitant was significantly more frequent (78.6% vs 69.7%, p < 0,001). All cases of ifosfamide-induced encephalopathy occurred after an infusion time greater than or equal to 12 hours.

Ifosfamide EG was introduced in March 2015 and April 2016 at the respective sites, when the ANSM issued a notice to health care professionals to inform them about the reduced shelf life of the solution formulation. These measures might have led to an increased reporting of encephalopathies for Ifosfamide EG. As the data about diagnosis for IIE was obtained from the pharmacovigilance centres in France and not from the patient records, a change in reporting behaviour during the course of the study could have had an impact on the study results.

In conclusion, the study shows a significant difference in encephalopathy incidence between the Holoxan cohort and the Ifosfamide EG cohort with a notably low incidence in the Holoxan arm. However, the incidence reported in the Ifosfamide EG arm is also low compared to other studies. Awareness to the risk of encephalopathy in particular with Ifosfamide EG, was increased shortly after or at the time when it was introduced in those centres, which may have impacted reporting of encephalopathy. The value of this study for the evaluation of a possible risk difference between the products is thus limited.

2.2.2.2.3. Filhon 2016 study

A retrospective study compared the occurrence of IIE according to the formulation used in 55 children, using hospital records in one centre from 2010 to 2015 (Filhon, 2016)[14]. There were five episodes of IIE reported out of 116 (4.3%) courses of Holoxan and 24 episodes out of 114 (21.1%) courses for Ifosfamide EG. The OR (95%CI) for Ifosfamide EG was 5.9 (2.2– 16.1).

Out of the 55 children included in this study, 19 patients experienced 31 episodes of encephalopathy. The number of patients treated with a product and the number of patients developing an encephalopathy during treatment were not provided separately for the respective treatment cohorts.

No information on distribution of indication or used treatment regimen between the cohorts was provided. Although the authors state that the treatment protocol with ifosfamide did not change during the 5-year study period an imbalance of indications cannot be excluded and might confound the observed frequency in encephalopathies. Indeed, in 4 of 116 courses for Holoxan (3.4%) and in 38 of 114 courses of Ifosfamide EG (33%) the patients had pelvic/renal location, which indicate a difference in the treated patient population (p < 0.001). The number of patients presenting with pelvic/renal location was not provided, nor was information on the number of patient with pelvic/renal location developing IIE. Pelvic disease as well as an impaired renal function have been identified as risk factors for the development of IIE. The Holoxan and Ifosfamide EG group are not directly comparable in this study. Information is also missing on patient's treatment history, concomitant drug exposure, re-challenge with ifosfamide, re-occurrence of encephalopathy episodes in individual patients and the diagnostic criteria for encephalopathy are unclear.

In conclusion, this study observed an increased risk for encephalopathies in patients treated with Ifosfamide EG, but the data are limited by the small number of patients and the significantly different distribution of risk factors between the cohorts. In addition, it lacks important information to evaluate the data (e.g. number of patients included in each cohort, indications for treatment).

2.2.2.2.4. Lee 2011 case series

A series of 13 paediatric cases (age 4-19) at five sites in the United States reported IIE after treatment with the solution formulation between 2002 and 2010 (Lee, 2011)[39]. Five patients were re-challenged with the powder formulation, without recurrence of neurotoxicity. One of these five patients received a reduced dose. Another patient was re-challenged with a reduced dose of the solution formulation without recurrence of neurotoxicity. All other patients discontinued treatment. The authors concluded that their results suggest a possible increased incidence of ifosfamide neurotoxicity with the liquid formulation of the medicinal product.

The authors do not report that any positive re-challenge occurred with either formulation. A negative re-challenge with one product does not postulate a risk for another product. Negative re-challenges have been reported in several studies after an IIE.

The number of all patients treated with liquid ifosfamide in the respective period has not been provided precluding any calculation of incidence and no data for the powder formulation has been reported as well. Therefore, it is not possible to assess whether 13 cases at 5 centres over 8 years are a high incidence, nor to make any statement about an increased incidence in comparison to the powder formulation.

No conclusion regarding an increased risk of encephalopathy in patients treated with liquid ifosfamide medications can be made based on the review of this case series.

2.2.2.2.5. Viard Gaudin 2016 study

A retrospective study compared the occurrence of IIE according to the formulation used in 99 patients, using patients charts in one centre from 2011 to mid-2015 (Viard Gaudin, 2016)[40]. It is not known whether the identified cases include only documented encephalopathies or whether they also include cases that report symptoms indicative of encephalopathy.

Fifty-seven (57) patients were treated in the Holoxan cohort (including 18 children) and 42 patients (including 13 children) in the Ifosfamide EG cohort. One (1) adult out of 57 patients in the Holoxan cohort (1.7%) and 13/42 patients (31%) including five children developed encephalopathy in the Ifosfamide EG cohort. The rate of encephalopathy reported after treatment with Holoxan is remarkably low. The occurrence of encephalopathy in the Ifosfamide EG cohort is high, but within ranges reported in the literature.

All but one case occurred in patients treated for sarcoma. Several possible risk factors were detected among the patients treated with ifosfamide (e.g. hypoalbuminemia, renal insufficiency). Neither the risk-factor distribution among the two treatment cohorts nor the distribution between patients with and without encephalopathy were presented or discussed. Hence, the impact of risk factors on the differences observed between the treatment cohorts remains unknown.

The remaining shelf life of the products causing encephalopathies was analysed to evaluate the hypothesis that encephalopathy is caused by degradation products, and that the risk increases with time since production. The author concluded that they confirmed the results of a previous national study as all lots causing encephalopathy were used 7 months after production. Considering that lots involved in this study had a shelf life of 18 and 24 months and that lots closer to the expiry date are distributed and used first, it is expectable that the products have been used 7 months or more after production. No data on the time since production of Ifosfamide EG preparations not causing

[39] Lee A. et.al. Ifosfamide Neurotoxicity in Paediatric Patients: A Multi-Institutional Case Series Report. J Hematol Oncol Pharm. 2011;1(3):12-17.
[40] Pharmaceutical theses by Gwendal Viard Gaudin. La spécialité Ifosfamide EG engendre-t-elle plus d'encéphalopathie que la spécialité Holoxan? Étude au CHU de Grenoble. Sciences pharmaceutiques. 2016.

encephalopathy was provided. Consequently, an association between time since production and the risk to develop encephalopathy cannot be evaluated.

In conclusion, although a clear difference is observed in encephalopathy rates between the Holoxan cohort and the Ifosfamide cohort, the data is difficult to interpret. The patient population is very small and important information for the evaluation of data, such as risk factors or diagnostic criteria for encephalopathy, is missing.

2.2.2.3. Data from other studies

The notification of a cluster of cases after the introduction of the solution formulation in France lead to the opening of a pharmacovigilance investigation in March 2015, as a result of which the below studies were conducted. These were not published in the scientific literature.

2.2.2.3.1. Official investigation of ifosfamide and central neurological effects Holoxan Baxter SAS Laboratory Ifosfamide EG EuroGenerics Laboratory, September 2015

A retrospective study compared the occurrence of IIE according to the formulation used, in cases of AEs in the MEdDRA system organ class (SOC) "nervous system disorders" and "psychiatric disorders" as well as the SMQ "encephalopathy" reported to the CRPVs, to the MAHs or in the national database between mid-2012 and mid-2015.

In total 186 cases were reported, including 50 for Holoxan, 125 for Ifosfamide EG and the invented name was not specified in the remaining of cases. There were more reports of paediatric cases (< 18 years) for Ifosfamide EG (n=62 (49.6%)) than for Holoxan (n=9 (18.0%)). Only cases have been analysed. Hence, it is not possible to evaluate whether the high percentage of paediatric patients developing neurotoxic symptoms is caused by an increased risk associated with the product or by a higher proportion of paediatric patients among the patients treated with Ifosfamide EG. It cannot be excluded that more oncopaediatric centres use Ifosfamide EG.

The authors conclude that more reports of serious cases were reported for Ifosfamide EG, but the information on the severity of the events is inconsistent. On one hand, 88% severe cases for Holoxan and 96% severe cases for Ifosfamide EG were reported. On the other hand, more fatal cases (14%) and more grade 3 and 4 events (92.5%) were reported for Holoxan in comparison to Ifosfamide EG (0.8% fatal cases and 86.6% Gr. 3 and 4).

Out of the cases, more patients had a sarcoma in those treated with Ifosfamide EG (74.4%) compared to those treated with Holoxan (64.0%), whereas this population is more likely to have risk factors for IIE (e.g. pelvic disease, high dose).

Although the authors made no analysis of the risk factors associated with co-prescriptions due to the lack of completeness of the data, it should be noted that the cases for Ifosfamide EG report a much higher use of antiemetic drugs (50.4%; 23.2% aprepitant and 20.8% alizapride) in comparison to Holoxan (14.0%; 14% aprepitant and 0% alizapride). It cannot be excluded, that the observed symptoms of encephalopathy were caused by antiemetic drugs or that the neurotoxicity of antiemetic drugs aggravates the neurotoxic effects of ifosfamide.

The reporting frequencies were analysed per gram of active substance sold each year. The rate thus calculated was stable until 2008 for Holoxan and a four-fold increase was observed from 2009 to 2013, whereas with Ifosfamide EG, from first marketing, it was higher in comparison. Considering the inter-individual variability of the cumulative ifosfamide dosage and the much higher proportion of paediatric patients in the Ifosfamide EG group, a frequency per gram of active substance is a poor proxy for a

frequency per patient and a difference between reporting frequencies has to be interpreted with caution.

In conclusion, the increase of reported encephalopathies/neurotoxicity after the market entry of Ifosfamide EG is of note, but the data is confounded by possible differences between the patient cohorts. Furthermore, due to the wide search strategy without apparent subsequent case selection, it is questionable whether all events were really encephalopathies. It is agreed with the authors of this study that the case analysis leads to the suspicion of a pharmacovigilance signal for Ifosfamide EG and that this signal would deserve to be validated by a more exhaustive study.

2.2.2.3.2. Pharmacovigilance investigation of undesirable central neurological effects such as encephalopathy under ifosfamide, February 2016

A survey of oncopaediatric centres was performed to evaluate the signal suspected further to the above results. No information on the methods used was available. The below results show that analyses were performed for cases of encephalopathy in patients treated with either formulation of ifosfamide: for all cases received by French pharmacovigilance centres (CRPV) and for cases reviewed retrospectively for whom usage data was available. It is not known however if the analysis concerned strictly cases of encephalopathy or, as for the previous study, all cases of neurotoxicity.

Table 2. Ifosfamide induced encephalopathy or neurotoxicity in oncopaediatric centres

Exhaustive data (consumption indicated + retrospective study)

	2010		2011		2012		2013		2014		2015		2010-2015	
	H	EG	H	EG	H	EG	H	EG	H	EG	H	EG	H	EG
Number of CRPVs (consumption indicated + retrospective collection)	6		8		9		11		10		8			
Consumption in g	2421	0	3278	0	2234	0	1265	2987	75	3196	781	1707	10054	7890
Number of cases*	3	0	3	0	6	0	1	14	0	22	1	7	14	43
Number of episodes **	4	0	4	0	6	0	1	26	0	34	1	8	16	68
Incidence of number of cases (per g)	1/807	0	1/1093	0	1/372	0	1/1265	1/213	0	1/145	1/781	1/244	1/718	1/183
Incidence of number of episodes (per g)	1/605	0	1/820	0	1/372	0	1/1265	1/115	0	1/94	1/781	1/213	1/628	1/116

3.9 times more children had an episode of encephalopathy with EG
5.9 times more encephalopathy episodes with EG

Spontaneous notification data

	2010		2011		2012		2013		2014		2015		2010-2015	
	H	EG	H	EG	H	EG	H	EG	H	EG	H	EG	H	EG
Number of CRPVs (consumption indicated + spontaneous notification or collection method not indicated)	12		14		15		11		15		17			
Consumption in g	5622	0	5689	0	6101	0	3149	2545	6950	3385	4877	4075	32388	10005
Number of cases*	0	0	4	0	2	0	2	0	0	20	3	18	11	38
Number of episodes **	0	0	4	0	2	0	2	0	0	31	4	20	12	51
Incidence of number of cases (per g)	0	0	1/1422	0	1/3051	0	1/1575	0	0	1/169	1/1626	1/226	1/2944	1/263
Incidence of number of episodes (per g)	0	0	1/1422	0	1/3051	0	1/1575	0	0	1/109	1/1219	1/204	1/2695	1/196

The authors concluded that the signal is confirmed as, based on the dataset prepared further to patient record review, 4 times as many children developed an encephalopathy on Ifosfamide EG in comparison to Holoxan.

Patient numbers have not been reported, only the amount of ifosfamide used in paediatric patients. A higher proportion of Ifosfamide EG has been included in the retrospective review (7,890 g of 17,895 g (44%) vs. 10,054 g of 42,443 g (24%) for Holoxan). Looking specifically at the years where the consumption of both medicinal products was reported (2013-2015), a greater difference is noted as 12% (2,121 g of 17,097 g) of the Holoxan consumption is included in the retrospective review compared to 44% (7,890 g of 17,895 g) of the ifosfamide EG consumption. In particular in 2014, the year most encephalopathies have been reported in the retrospective review, hardly any patients treated with Holoxan were included (75 g vs. 3196 g for Ifosfamide EG).

Missing information on methodology, the suspected combination of spontaneously reported data and data from reviewed medical records, a possible misbalance between the used data sources for Holoxan and Ifosfamide EG and the lack of many relevant information (e.g. patient numbers, risk factors) preclude the interpretation of this data.

The impact of the shelf-life of ifosfamide EG on the development of encephalopathies has been analysed in a group of 44 patients, including 17 with at least one episode of IIE. The median shelf life was 8.9 months [7.4-10.1] in the group which experienced encephalopathy and 8.3 months [7.7-11.0] in the group that did not. Lots that were analysed appeared to be within the specification during the first 18 months after production.

2.3. Quality and toxicological aspects

2.3.1. Quality

Taking into consideration the composition (including excipient qualities), manufacturing process/equipment, bulk storage (including bulk storage packaging material) and finished product primary packaging material, the 40 mg/ml finished product is identical in both MS where it is authorised. In addition to the active substance ifosfamide, the finished products contain the usual excipients for isotonization, buffering and pH adjustment; the concentrate additionally contains urea as a solubilizer.

The impurity profile of the 40 mg/mL and the 200 mg/mL ifosfamide containing solutions appears to be similar with the exception of Impurity rRf~4.3. This impurity is formed in presence of urea, thus only in the concentrate formulation, which is not authorised in France. Therefore, this impurity would not explain the increased reporting of encephalopathy in France with the solution formulation.

The handling of the finished products until administration to patients, e.g. storage conditions, transport conditions/times is also the same in both MS. The only differences are the shelf-life of the finished product and the in-use shelf-life of the diluted solutions at ambient temperatures (0.9% sodium chloride solution and 5% glucose solution). Indeed, as mentioned the shelf life of the finished product was shortened from 18 months to 7 as a precautionary measure in May 2016, in France only.

The submitted results of the batch analysis are in accordance with the specification and indicate a uniform batch quality.

The quality of the product was reviewed, with a view of identifying impurities present in the finished product at higher levels at the time of administration of the final solution than at release, whether or not they are additionally metabolites. The specification limits for impurities at release and during shelf life are in accordance with quality guidelines and are acceptable.

Three in-use stability studies have been performed on a 19 months old 40 mg/ml batch diluted to 4 mg/ml in a glucose solution, a saline solution or a in water for injection (this last one was only performed for the first of the below conditions) for:

- 24 hours at 2-8°C followed by a further 4 days at 25°C/ 60% relative humidity (RH)

- 4 days at 2-8°C

- 4 days at 25°C/ 60% RH

Impurity A, Impurity C, Impurity rRf~1.1, Impurity rRf~1.4, Impurity rRf~4.3, Impurity rrt~0.4 have thus been identified as relevant.

Toxicological qualification/justification relating to Impurity C (Ph. Eur.), Impurity rRf~1.1 (TLC), Impurity rRf~1.4 (TLC) and Impurity rrt~0.4 (HPLC) has been provided (please see 2.3.2.).

Additional qualification/justification relating to impurity A (Ph. Eur.) has not been provided nor requested since the limit is the same as the Ph. Eur. monograph for ifosfamide and as such considered qualified. This impurity was found above the specification limit during "worst case" in-use studies (see also below). However, rather than qualifying a higher limit in line with the results of the worst case in use studies it is considered more appropriate to shorten the in-use shelf life, in order for impurity A to remain below the current limit.

Out-of-specification (OOS) results were recorded in the worst-case studies, notably for the product diluted with 0.9% saline solution after 4 days at 2-8°C for Impurity A and at 25°C for Impurity rRf~ 1.1 and rRf~1.4. Of note, no OOS were noted for those three impurities up to day 4 under the first testing conditions, however OOS were noted from day 3 for single unknown impurity.

According to those results, the in-use shelf life may need to be lowered as indicated below.

Storage at 2-8°C: 4 days when prepared for use with 5% glucose solution. Do not store when prepared for use with 0.9% sodium chloride solution.

Storage at 25°C: 2 days when prepared for use with 5% glucose or 0.9% sodium chloride solution.

However, the data available at present on a single batch does not allow to conclude with certainty on the adequate shelf lives and storage conditions. The MAH is therefore required to submit the results of in-use stability studies to the NCAs within the agreed timeframe, in order to determine appropriate shelf life, storage conditions for the product and diluted solutions, and for appropriate information to be reflected in the product information in this regard.

Considering that these out of specifications results occurred no sooner than 19 months from release and a day in diluted solution, it would not explain the results observed in France for encephalopathy reports, even more so after the precautionary self-life reduction to 7 months.

Based on the submitted quality data, it is not possible to conclude that the quality of the medicinal products in question would cause an increased risk for IIE with ifosfamide EG solution for infusion compared with ifosfamide powder for solution.

2.3.2. Toxicology

2.3.2.1. Impurity C

Impurity C (2-chloroethylamine, CEA) is specified as an impurity in the finished product with a maximum concentration of 1%. Impurity C is also a metabolite. The formation of 2-chloroethylamine *in vitro* and *in vivo* following ifosfamide administration to humans and its detection in the urine has repeatedly been described. *In vivo* 2-chloroethylamine was detected in plasma following ifosfamide

dosing (Momerency, 1994)[41]. *In vivo* peak 2-chloroethylamine /ifosfamide ratios of 50.2% and 50.1% (w/w) after intravenous administration indicate that chemical hydrolysis is significant in the plasma at body temperature (Highley, 1995)[42]. Corresponding values after oral dosing are 4.9% and 8.2% (w/w). In addition, the recovery of 2-chloroethylamine in urine was 12.7 ± 6.7 % and 6.5 ± 3.3 % after intravenous and oral dosing respectively, expressed as a percentage of the ifosfamide dose (Aeschlimann, 1998)[37]. A later study further confirmed this finding, as approximately 5% 2-chloroethylamine was generated from the ifosfamide dose after oral ifosfamide intake (Highley, 2015)[43].

Therefore, the amount of 2-chloroethylamine impurity is considered of negligible importance compared to levels formed *in vivo*. Hence, according to the above-mentioned findings the impurity 2-chloroethylamine seems not to be a major contributor to ifosfamide neurotoxicity.

2.3.2.2. Other impurities

Impurity rRf~1.1, rRf~1.4 and rrt~0.4 occur in Ifosfamide EG 40 mg/mL solution for infusion and increase during shelf life. No literature data was identified in order to toxicologically qualified these impurities. Therefore, *in silico* methods were used.

Ifosfamide, rrt~0.4, rRf~1.1 and rRf~1.4 triggered no alerts for neurotoxicity.

The impurity rrt~0.4 triggered an alert for mitochondrial dysfunction. It cannot be ruled out, that the impurity rrt~0.4 may also contribute to mitochondrial dysfunction that could lead to neurotoxicity. The inhibition of intra- and extramitochondrial NADH oxidation by rrt~0.4 could affect the intracellular NAD/NADH ratio, and large quantities of aldehydes, such as aldo-ifosfamide, acrolein and chloroacetaldehyde, might be formed, just as ifosfamide does this itself. Considering that the possible mechanism via mitochondrial dysfunction of rrt~0.4 seems similar to that of ifosfamide the above-mentioned findings of rrt~0.4 seems not to be a major contributor to ifosfamide neurotoxicity. However, it cannot be ruled out that it could play a role in causing neurotoxicity.

The two impurities, rRf~1.1 and rRf~1.4 triggered an alert for nephrotoxicity. Ifosfamide, rrt~0.4 and rRf~1.1 triggered alerts for teratogenicity and ifosfamide as well as rrt~0.4 triggered an alert for Cholinesterase inhibition.

No toxicological assessment was considered necessary for impurity A as the specification limit both at release and end of self-life is the same as the Ph. Eur. Limit for the active substance.

2.4. Discussion

2.4.1. Ifosfamide induced encephalopathies

Ifosfamide is known to carry a risk of CNS toxicity, including encephalopathies. The frequency of IIE reported in the literature varies between 10% and 30%. The suspected causes of encephalopathy are the metabolites chloroacetaldehyde and chloroethylamine.

The PRAC noted that routine risk minimisation measures across the different PI of the solution formulations were inconsistent. Taking into account all available information on CNS toxicity with this active substance, the PRAC considered that existing warnings in section 4.4 should be revised as

[41] Momerency G et al. The determination of ifosfamide and seven metabolites in blood plasma as stable trifluoroacetyl derivatives by electron capture chemical ionisation GC-MS. J. High Resoln. Chromatogr. 1994; 17: 655-661
[42] Highley M S, Momerency G, Van Cauwenberghe K, et al. (1995): Formation of Chloroethylamine and 1,3 Oxazolidine-2-one following Ifosfamide Administration in Humans. Drug Metabolism and Disposition Vol. 23, No.3
[43] Highley MS et al. The Neurotoxicity and Pharmacokinetics of Oral Ifosfamide. Journal of Analytical Oncology 4(1): 13-23 (2015)

relevant to reflect the fact that this toxicity may become manifest within a few hours to a few days after administration. If 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. Any reference to the toxicity occurring after the first administration should be removed, as it may also develop after the second or subsequent treatment cycles.

The following possible symptoms should be reflected: confusion, somnolence, coma, hallucination, blurred vision, psychotic behaviour, extrapyramidal symptoms, urinary incontinence and seizures.

Influencing factors should also be revised as whilst several possible risk factors have been discussed in single studies, case series or case reports, or conflicting results were reported, only those confirmed in several independent studies are considered relevant to be mentioned. Studies suggest that CNS toxicity would be dose dependent. Further, whilst other risk factors cannot be categorically excluded, the following are considered confirmed: hypoalbuminaemia, impaired renal function, poor performance status, pelvic disease and previous or concomitant nephrotoxic treatments including cisplatin. Evidence on the effect of the duration of infusion is inconclusive and no guidance can be provided in this regard.

Concomitant use of aprepitant was discussed in case series, but no statistical association was found in retrospective studies. Nevertheless, the PI should also warn 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.

No comparative study investigating differences between adults and paediatric patients is available and, overall, data on risk factors in the paediatric population is very limited. Overall, the metabolism of ifosfamide and risk factors for encephalopathy seem to be comparable in children and adults and a wide inter-individual variability in all age groups is noted.

Methylene blue is mentioned as a possible treatment for encephalopathy, and whilst its efficacy remains unclear, PRAC considered that healthcare professionals (HCP) should nonetheless be informed that it could be considered for the treatment and prophylaxis of ifosfamide-associated encephalopathies. Considering that encephalopathies occur at recommended doses of ifosfamide, its management should be covered under the dedicated warning and is not relevant for section 4.9 of the SmPC.

Information not related to CNS toxicity should not be reflected under this particular subheading/warning and the MAHs are reminded of the obligation to maintain their product information up to date in accordance with Article 23 of Directive 2001/83/EC, including in line with information included in the PI of the reference medicinal product.

2.4.2. Safety studies suggesting a possible excess risk of IIE with solutions

A search in EV identified 434 cases of encephalopathy associated with ifosfamide treatment in the EEA. Of these cases, 393 occurred in France (including 229 with the solutions) and 11 in Germany (including 1 with the solution). Of note the use of the solution formulations is approximately 3 times greater in Germany than in France (i.e. 3,000 patients-years vs 1,000 patient-years). Ifosfamide is mostly given according to established treatment protocols and current treatment guidelines and no relevant difference in term of indications or posology was identified in the PI across MS that could explain the different reporting. This difference can be partly explained by the stimulated reporting in France due to the national investigations of a possible increased risk with the solutions compared to the powder formulation initiated in 2014. Considering the limited information available on indication, medical

history or concomitant medication, no additional factor that could contribute to the different reporting rate could be identified.

No data from prospective clinical trials comparing different ifosfamide-containing products is available. A number of retrospective studies have however been performed and suggested an increased risk for IIE with ifosfamide EG solution for infusion compared with ifosfamide powder for solution. However, as described below, limitations have been identified to these studies, thus precluding definite conclusions.

Further to the national investigations in France, the shelf life of the ifosfamide solution was lowered in that MS as a precaution from 18 to 7 months in 2016. A case control study was then performed, to evaluate the impact of this measure, based on data from medical record of all children treated with any ifosfamide formulation in paediatric oncology departments. The authors found an increased risk of encephalopathy associated with ifosfamide 7-month shelf-life liquid formulation compared to lyophilised powder (adjusted OR: 1.91; 95%CI [1.03-3.53]). These results should be interpreted cautiously in view of the lack of precision of the point estimate. Differences were noted between groups in term of diagnosis and treatment protocol, indicating that more patients with sarcoma and especially Ewing-sarcoma patients, with a high risk for pelvic disease, were treated with the solution formulation. Whilst pelvic disease is a risk factors for IIE, it is noted that adjustment by age, gender and indication (sarcoma) had a negligible effect on the Odd Ratio which supports that confounding by indication may be low. However, dose-dependent effects may be present, as 42.8% (8/14) of the patients treated with Ifosfamide EG who developed IIE received high-dose treatment cycle(s), compared to 13.0% (6/26) of the patients treated with Holoxan. As the controls have not been analysed, it is not known whether the differences between the cases reflect differences between the whole cohorts. As with all observational studies, residual confounding due to unmeasured confounding of the study results cannot be excluded. This is particularly relevant in the present case, as several known risk factors were not considered in this study, such as previous treatment with cisplatin or hypoalbuminemia. In light of these limitations and the low precision of the risk estimate, the study is not considered sufficient to conclude on an increased risk for encephalopathies in patients treated with Ifosfamide EG.

A retrospective study in adults between 2013 and 2017 also found a statistically significant difference in IIE between patients treated with Holoxan 1.9% (2/103) against 10.2% (9/88) in the Ifosfamide EG group ($p = 0.014$). It is noted that the reporting rate in patients treated with Holoxan is particularly low, compared to those reported in the literature. Of note, data was obtained from pharmacovigilance centre and not directly from patient records. Considering that both study centres switched from Holoxan to Ifosfamide EG over 2015-2016, time around which HCP were informed about the precautionary shelf-life reduction for Ifosfamide EG, the results might have been impacted by change in reporting behaviour due to an increased awareness of the risk of encephalopathies.

Imbalances in occurrence of IIE or neurotoxic symptoms depending on the formulation used were also noted in earlier studies performed in France to investigate this issue. A first study found that between June 2012 and September 2015 more cases with AEs in the SOC Nervous system disorders, the SOC Psychiatric disorders and the SMQ Encephalopathy had been reported in the national database for patients treated with Ifosfamide EG (n=125) than for those treated with Holoxan (n=50). About half the cases with Ifosfamide EG occurred in children, whereas this represented around a fifth of the cases with Holoxan. As only the cases were analysed, it is not possible to appreciate whether this reflects a higher usage of the solution formulation in paediatric patients or an increased risk of neurotoxicity in this population. In the Ifosfamide EG cases 10% more patients were treated for sarcoma, which is a known risk factor. In addition, among Ifosfamide EG cases more patients were given antiemetics, which are known to carry a risk of psychiatric and nervous system disorders. In conclusion, it cannot be excluded, that the observed differences in developing encephalopathy/neurotoxicity were

confounded by differences between the cohorts (e.g. age, concomitant medication, diagnosis). Furthermore, due to the wide search strategy it is questionable whether all events were encephalopathies.

As a follow up a survey in oncopaediatric centres was performed and found that 4 times as many children developed encephalopathy on Ifosfamide EG in comparison to Holoxan. However, information is missing on methodology, on the number of patients, patients' characteristics and other possible risk factors. It is not known either whether results relate to encephalopathy strictly, or as in the previous study to neurotoxicity. Further, a higher amount of Ifosfamide EG consumption has been included in the retrospective study, in particular in 2014 where the most encephalopathies have been reported, hardly any patients treated with Holoxan were included. These results are considered too limited to draw a conclusion on a potentially increased risk for encephalopathies.

Further monocentric studies and a case series did not provide additional relevant information.

In conclusion, 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.

2.4.3. Quality and toxicology aspects

Looking at the quality of the solutions products, the 40 mg/ml finished product is largely identical in both MS. The impurity profile of the 40 mg/mL and the 200 mg/mL ifosfamide containing solutions appears to be similar with the exception of an impurity forming only in the concentrate formulation, which is not authorised in France and therefore, would not explain the increased reporting of encephalopathy in France with the solution formulation. The submitted results of the batch analysis are in accordance with the specification and indicate a uniform batch quality. The quality of the product was reviewed, with a view of identifying impurities present in the finished product at higher levels at the time of administration of the final solution than at release, whether or not they are additionally metabolites. Six impurities were identified as relevant and toxicological qualification/justification provided for 5 of them. No toxicological assessment was considered needed for the last one as the specification limit both at release and end of self-life is the same as the Ph. Eur. Limit for the active substance. No literature data was available for three of the impurities, using *in silico* methods, it could not be ruled out, that one may also contribute to mitochondrial dysfunction that could lead to neurotoxicity. However, as this would be mediated through the same mechanisms than ifosfamide itself, it is considered unlikely to be a major contributor to the neurotoxicity. The last one, impurity C, is also a metabolite and the amount of the impurity are negligible compared to levels formed *in vivo*, hence this impurity is not considered to be a major contributor to ifosfamide neurotoxicity either.

Therefore, it is not possible to conclude that the quality of the medicinal products in question would cause an increased risk for IIE with ifosfamide EG solution for infusion compared with ifosfamide powder for solution.

It was noted however that OOS results were recorded in the worst-case studies, notably for the product diluted with 0.9% saline solution. According to those results, the in-use shelf life should be lowered, however, data from further batches would be needed in order to conclude on the adequate shelf lives and storage condition. The MAH is therefore required to submit the results of in-use stability studies to the NCAs within the agreed timeframe, in order to determine appropriate shelf life, storage conditions for the product and diluted solutions, and for appropriate information to be reflected in the product information in this regard. Considering that these OOS results occurred no sooner than 19 months from release and a day in diluted solution, it would not explain the encephalopathy reporting observed in France.

2.4.4. Pharmacovigilance activities

The PRAC considered whether additional pharmacovigilance activities would be useful to generate data allowing to elucidate this issue. In particular, the feasibility of studies on medical records to further investigate the encephalopathy reporting rates depending on formulation, taking into account the caveat highlighted above was considered. A further paediatric study in France would include to a large extent the same medical records than the study already performed by Hillaire-Buys and colleagues as almost all university hospitals were included, and the product was withdrawn from the French market shortly thereafter. This would allow a better description of the whole cohorts treated with either formulations. However, it remains uncertain whether this would overcome the limitations of the 2019 study, as the differences between the IIE cases in both cohorts would remain (e.g. in term of treatment protocol, cumulative dose). Further, adequately controlling for risk factors in the analysis would be impeded by their high number for a relatively low number of encephalopathy cases (18 cases in the ifosfamide EG arm). An alternative would be a study in adults, however more IIE risk factors are expected in adults (e.g. decreased renal function, concomitant medication). Thus, this would not be expected to overcome the issue highlighted either. A third option considered was the conduct of an equivalent study, but in Germany, however the same difficulties would be faced. Finally, data from available registers is not detailed enough to evaluate this issue. In conclusion, 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.

3. Benefit-risk balance

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%.

This review was initiated further to epidemiological studies suggesting 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). The scope of this procedure is limited to solutions and concentrates for solutions, herein commonly referred to as 'solutions'.

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 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.

4. Summary of new activities and measures

4.1. Risk management

4.1.1. Risk minimisation measures

4.1.1.1. Routine risk minimisation measures

Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the risk of CNS toxicity, including encephalopathy, associated with the use of ifosfamide-solutions. These changes include amendments to sections 4.4 of the SmPC.

Warnings and precautions of use relating to the risk of encephalopathy and CNS toxicity associated with the use of ifosfamide were brought up to date.

The Package Leaflet was amended accordingly as relevant.

Conflicting information on the risk of encephalopathy and CNS toxicity included in other sections of the product information should be removed.

For other sections, the MAHs are also reminded of the obligation to maintain their product information up to date in accordance with Article 23 of Directive 2001/83/EC, including in line with information included in the PI of the reference medicinal product.

4.2. Quality studies

The MAH(s) shall perform in-use stability studies in line with current stability guidelines. While only the shelf life of the prepared solutions before administration is considered in CPMP/QWP/159/96 (Note for guidance on maximum shelf-life for sterile products for human use after first opening or following reconstitution), the MAH is recommended to include the duration of the administration process itself (24 hours in case of continuous infusion as stated in SmPC) in the "in-use stability testing protocol". In order to allow for comparison of test results relating to 5% glucose solution and 0.9% sodium chloride solution, related samples should have the same impurity levels at the beginning of the in-use study (t=0).

The results of these studies shall be submitted for assessment to the relevant National Competent Authorities within the agreed timeframe. The MAH is advised to submit those via a worksharing variation. A discussion of the dilution in 0.9% NaCl should be provided. New shelf life, storage conditions for the product and diluted solutions should be proposed in line with the results of the studies. In addition, updates to the package leaflet should be proposed in order to include a dedicated section to healthcare professionals on handling of ifosfamide solutions, including storage conditions and conditions of use after dilution, in line with information in section 6.3, 6.4 and 6.6 of the SmPC.

5. Condition to the marketing authorisations

The marketing authorisation holder(s) shall complete the below conditions, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

The MAH(s) shall perform in-use stability studies and submit the results to the relevant National Competent Authorities for assessment by:	30 September 2021

6. Grounds for 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.

Appendix 1

Divergent position

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 PRAC 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 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

PRAC Member expressing a divergent opinion:

- Adrien Inoubli (FR)