12 March 2020
EMA/PRAC/111337/2020

PRAC List of questions

To be addressed by the marketing authorisation holders for ifosfamide-containing solutions

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

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

INN/active substance: ifosfamide

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1. Questions

The marketing authorisation holders MAH(s) of solution or concentrate for solution medicinal products containing ifosfamide, are requested to address the following questions for their products:

Question 1. Please provide in the annexed table:

a) Information on marketing status and on drugs substance and drug products manufacturers.

b) An overview of the estimated sales figures and patient exposure for in each EEA country and the total exposure in the EEA per year and cumulatively from 01 January 2012 until 29 February 2020. Patient exposure should be expressed in number of patients and patient-treatment-years per product. Please indicate your method of calculation specifying the assumptions made for dose and duration of treatment.

c) An overview of the approved indication(s) and information included in the summary of product characteristics (SmPC) and package leaflet (PL) on posology, regarding the risks of encephalopathy, storage conditions and stability of the reconstituted solution and prepared infusion.

Safety

Question 2. Please provide:

a) The number of encephalopathy cases reported in the MAH's safety database, searching with the SMQ Non-infectious encephalopathies/delirium since 2012. The data should be presented both for the narrow and for the broad SMQ, for each age group (0-6 years old, 6-12 years old, 12-18 years old and 18 years of age and older) in each EEA Member State and in total in the EEA.

b) A review and critical discussion of clinical trial data (including both MAH sponsored and non-sponsored studies), pharmaco-epidemiological studies and literature that report data on encephalopathies for your ifosfamide-containing solutions in comparison to powder for solutions formulations of ifosfamide-containing medicinal products, including but not limited to the publications by Hillaire-Buys 2019 [1] and Chambord 2019 [2].

c) A discussion, for impurities and degradation products considered as metabolites, of the expected exposure in human in relation to the expected formation *in vivo* (see questions 4 and 5).

Question 3. Discuss the possible mechanism(s) for ifosfamide-induced encephalopathy and discuss possible risk factors for developing such encephalopathy. Discuss potential differences in sensitivity for development of encephalopathy among children and adults following ifosfamide exposure. This should include potential differences in general metabolism of these substances between children and adults.

Quality

Question 4. Please provide:

[1] 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. Therapie. 2019 Oct 28. pii: S0040-5957(19)30153-2

[2] Chambord J, Henny F, Salleron J, et al. Ifosfamide-induced encephalopathy: Brand-name (HOLOXAN®) vs generic formulation (IFOSFAMIDE EG®). J Clin Pharm Ther. 2019 Jun;44(3):372-380.

a) The specifications in force for the drug substance, drug product at time of release, drug product during shelf-life and (if different) after preparation of solution (in-use specification) together with the justifications for the limits of impurities in these specifications based on *in silico*, *in vitro*, and *in vivo* toxicological data.

b) Composition of drug products should be presented including solvents, process aids etc. used for drug products production, if applicable.

c) A discussion on both actual and theoretical impurities as well as those considered as metabolites (name and chemical formula should be presented). This discussion should cover how the impurities are formed (e.g. reagent, process-related, degradation, metabolism). The discussion should cover data on extractables/leachables in drug product, if applicable.

d) A discussion on theoretical worst-case degradation impurities values (percent) in the drug product considering drug product release limit plus increase during whole shelf-life plus increase after first opening (if applicable) and increase during maximum holding of diluted solutions additive.

e) Batch analyses from all drug product manufacturers. All results from the last three years or the last 20 batches from each manufacturer should be included. The results of levels of impurities should be presented in tabular format. Names and structure of known/identified impurities should be indicated.

f) Batch analysis data of the reference drug product and the reference drug product after reconstitution and dilution, as available.

g) Impurity profile comparison between solution form, concentrate for solution form and, as available, powder form of ifosfamide drug products. The comparison should include final drug product as well as drug product after dilution and reconstitution/dilution according to drug product's SmPCs (up to maximum holding times). Discussion relating to differences between solutions and concentrate for solutions drug product impurity profile and powder for solutions drug product impurity profile.

h) Confirmation that during analytical method validation, specificity stress testing peak purity of ifosfamide peak and peaks of impurities limited above qualification threshold has been ensured. It has to be ensured, that unspecified degradation products do not co-eluate with the related impurities specified above qualification threshold.

i) Updated stability data including in-use stability data and the complete available long-term stability data.

j) Summary of 'out of specification' results from batch analyses and stability studies since 2010, if any these should be discussed.

Toxicology

Question 5. A toxicological assessment of the ifosfamide metabolites, impurities, degradants extractables and leachables, as applicable present in the drug substance, drug product and excipients should be presented. The MAH should also provide a discussion about their potential pharmacological, pharmacokinetic and toxicological effects and all available *in silico*, *in vitro* and *in vivo* studies. A special emphasis should be put on possible transfer of identified impurities and metabolites through blood-brain barrier as well as the potential neurotoxicity of these substances.

Benefit-risk balance and risk minimisation measures

Question 6. Please provide details of any specific measure(s) that have already been taken in order to minimise the risk of encephalopathy in patients treated with ifosfamide-containing medicinal product(s) and comment on the effectiveness of such measure(s).

Question 7. Provide a full benefit-risk balance assessment of your ifosfamide-containing solutions in the currently approved indication(s) in the EU. This should include an assessment on the impact of occurrence of encephalopathies, considering your answers to the above questions, on the benefit-risk balance.

Question 8. Please provide proposals and justifications with supportive evidence for any risk minimisation measures (including changes to the SmPC/PL or to quality aspects) which may improve the benefit-risk balance of ifosfamide-containing solutions and how their effectiveness should be monitored.

2. Additional data review

As part of this review, the PRAC considers it necessary to perform a EudraVigilance analysis of encephalopathies with ifosfamide containing medicinal products. The data to perform this analysis will be provided by EMA and will be evaluated by PRAC together with the responses to the list of questions provided by the MAHs. This EudraVigilance analysis will be provided to all MAHs together with the preliminary assessment reports.

Annex

Question 1

a)

Product name	Marketing status	Pharmaceutical forms and strengths	Manufacturer(s) (name and full address)	Sales figures	Estimated patient exposure[1]

[1]. Expressed in patient years and stratified by Member State, by indication and by age (0-6 years old, 6-12 years old, 12-18 years old and 18 years of age and older). Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided.

b)

PI	SmPC	PL	Main differences in SmPCs/PLs between the different EU Member States
Overview of authorised indications			
Posology			
Information on encephalopathy in the relevant sections			
Storage conditions and stability of the reconstituted solution			
Storage conditions and stability of the prepared infusion.			