Benefits of ifosfamide solutions continue to outweigh risks

13.05.2021 | Circular Number P05/2021

Information on Ifosfamide

- Ifosfamide is used to treat several cancers, including various solid tumours and lymphomas. It is given into a vein and has been authorised as a ready-made solution, a concentrate for solution and a powder to prepare a solution for infusion in Germany and France. In most other EU Member States it is only available as powder for solution for infusion. Flucytosine is an antifungal agent, related to fluorouracil, which is used to treat systemic yeast and fungal infections.
- It may also be used with amphotericin in a synergistic combination to treat severe systemic candidiasis and in other severe or long-standing infection as well as cryptococcal meningitis.

  The following product is authorised via national procedure.

Active Ingredients	Product Name	Pharmaceutical Form	Classif-cation	Authorisation Number	MAH/license holder
IFOSFAMIDE 2 gram(s)	Mitoxana 2g Powder for Sterile Concentrate	Powder for concentrate for solution for infusion or injection	POM	MA1277/00701	Baxter Holding B.V.

Information from the EMA about the safety concern

- On the 11 March 2021, the EMA's safety committee (PRAC) concluded that the benefits of ifosfamide solutions for infusion continue to outweigh their risks in the treatment of different types of cancers, including various solid tumours and blood cancers such as lymphomas (cancer of white blood cells). The PRAC review was started because two recent studies[1,2] suggested that the risk of encephalopathy (brain disorders) with ifosfamide supplied in solution forms is higher than with the powder form. Ifosfamide-induced encephalopathy is a very common, known risk and is generally reversible.
- PRAC considered all available data and 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.
- PRAC recommended that the existing warning on ifosfamide-induced encephalopathy in the product information should be updated with the latest information on this side effect, including its characteristics and risk factors, as well as highlighting the need to closely monitor patients.
- A European Commission decision on this opinion will be issued in due course.
- Companies that market ifosfamide supplied as a solution will be required to carry out studies investigating the stability of the medicines in order to establish the optimal storage conditions

This review of ifosfamide-containing medicines was initiated at the request of the French Medicines Agency, under Article 31 of Directive 2001/83/EC. The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted its position.

As the CMDh position was adopted by majority vote, the CMDh position will now be sent to the European Commission, which will take an EU-wide legally binding decision in due course.

[1] Hillaire-Buys D, Mousset M, Allouchery M, et al. Liquid formulation of ifosfamide increased risk of encephalopathy: A case-control study in a pediatric population. Therapies [Online]. 2019 https://doi.org/10.1016/j.therap.2019.08.001

[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;44:372–380. https://doi.org/10.1111/jcpt.12823

In Malta

For Healthcare Professionals

- Administration of ifosfamide can cause encephalopathy and other neurotoxic effects; these known, very common side effects are generally reversible.
- A review of all available data on ifosfamide-induced encephalopathy concluded that an increased risk of encephalopathy with ifosfamide supplied as a solution could neither be confirmed nor ruled out due to limitations in the data.
- The existing warnings in section 4.4 (Special warnings and precautions for use) of the summary of product characteristics will be revised to include the following information:
  - Ifosfamide-induced CNS toxicity may appear within a few hours to a few days after administration and in most cases resolves within 48 to 72 hours of ifosfamide discontinuation. If CNS toxicity develops, administration of ifosfamide should be discontinued.
  - Patients should be closely monitored for symptoms of encephalopathy, in particular if patients are at increased risk for encephalopathy. Symptoms may include confusion, somnolence, coma, hallucination, blurred vision, psychotic behaviour, extrapyramidal symptoms, urinary incontinence and seizures.
  - CNS toxicity seems to be dose-dependent. Risk factors for the development of ifosfamide associated encephalopathy include hypoalbuminaemia, impaired renal function, poor performance status, pelvic disease and previous or concomitant nephrotoxic treatments including cisplatin.
  - Due to the potential for additive effects, medicines 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 ifosfamide-induced encephalopathy.

Advice for Patients

Treatment with ifosfamide

- Encephalopathy (brain disorders) is a very common, known side effect of ifosfamide and is generally reversible. Two recent studies have suggested that the use of ifosfamide solutions may increase the risk of this side effect compared with use of the powder form. However, an in-depth review of all available data could neither confirm nor rule out this increased risk.
- The package leaflet for these medicines will be updated with the latest information on factors that may increase the risk of encephalopathy and how to recognise signs of this side effect.
- Tell your doctor immediately if you experience confusion, sleepiness, unconsciousness, hallucinations, delusions (false beliefs), blurred vision, perception disorder (difficulty understanding information provided through the senses), problems with movement

such as muscle spasms or contractions, restlessness, slow or irregular movement, loss of bladder control and seizures (fits).

- Talk to your doctor before you are given an ifosfamide medicine if you have previously had treatment with another cancer medicine called cisplatin.

For more information please see the European Medicines Agency's press release.

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on ifosfamide medicinal products. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form and sending it to: Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 **or** online to http://www.medicinesauthority.gov.mt/adrportal or to the marketing authorisation holder or their local representatives.

Post-Licensing Directorate

Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health.

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this form (address side up), stapling the ends and then posting (no stamp required).

Feedback:

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