Background

Following the review of stability for cytotoxic drugs for the NHS tender, these monographs are designed to capture the information in a format that is useful for NHS aseptic units, particularly those working under Section 10 exemption with restricted shelf lives for products. There is also, where applicable, a view on the extended data beyond the maximum seven days that can be assigned under Section 10 exemption. This may be of use to licensed NHS aseptic units and also to procurement staff in terms of assessing the shelf lives assigned by commercial aseptic compounding units.

The studies provided have been reviewed against the standards of the NHS standards for stability testing of small molecule drug aseptic products[1].

Drug: **Ifosfamide Injection**

CMU requirements for shelf life (taken from Wave 12 tender)

7 days at 2 – 8°C at up to 20mg/ml in Sodium Chloride 0.9% infusion bags

British Pharmacopoeia specification for product.

BP2020 has a monograph for Ifosfamide for Injection

Ifosfamide for Injection is a sterile material consisting of Ifosfamide with or without excipients.

Content of ifosfamide - 95.0 to 105.0% of the stated amount.

Related substances (TLC test A degradation impurities, test B synthetic impurities)

- Impurity A < 0.25%
- Impurity C < 0.25%
- Impurity B < 0.15%
- Unassigned related substances < 0.15%

Assessment:

Manufacturer	SmPC shelf life	Excipients / formulation details	Assessment of Extended studies submitted	Shelf-life recommendation (section 10 units)	Comments on further shelf life extension
Baxter PL 00116/0392 PL 00116/0393	When prepared under strict aseptic conditions, ifosfamide is, as a 4% solution chemically stable for 7 days at room temperature with Water for Injections, 0.9% saline, dextrose/saline and dextrose solutions.	None	N/A but see below	SmPC shelf life seven days (recommended refrigeration at 2 – 8°C) for concentrations up to 40mg/ml in the choice of diluents listed.	See below
Drugsrus (Baxter product PI)	As above Baxter SmPCs submitted with tender	None	N/A but see below	SmPC shelf life seven days (recommended refrigeration at 2 – 8°C) for concentrations up to 40mg/ml in the choice of diluents listed.	See below

Conclusions (based on the data provided)

Additionally the Baxter SmPC currently states that: Ifosfamide and mesna when prepared under strict aseptic conditions at the recommended dilutions are chemically stable with:

(i) 0.9% saline and dextrose/saline solution for one week at room temp.
(ii) Water for Injections for one week under refrigeration.
(iii) 5% dextrose solution for 24 hours at room temperature, and
(iv) 0.9% saline solution for 28 days at room temperature.

However, a stability study carried out in early 2019[2] within Baxter has questioned this data particularly the 28 days with Mesna in Sodium chloride 0.9%, a further study is being undertaken in support of the regulatory submission to change the SmPC[3].

The active drug appeared relatively stable (from the loss of active viewpoint) although some losses were seen over the duration the more dilute solution was the least stable. Although all concentrations would have passed at day 14 based on loss of active alone, related substance C (2-chloroethanamine), levels of which determined the shelf life, is thought to be a substance of concern.

Data for Ifosfamide with Mesna was similar for Ifosfamide stability, also there were some issues reported with Mesna stability.

In accordance with the Baxter stability studies it is recommended that Ifosfamide and Ifosfamide in combination with Mesna is stored in a refrigerator in order to control the levels of degradation products. The shelf life at 2 – 8°C is recommended to be a maximum of seven days unless specific studies are available which included analysis of degradation products.

Published and other relevant reports

Physical and Chemical Stability of High-Dose Ifosfamide and Mesna for Prolonged 14-day Continuous Infusion, J Oncol Pharm Pract 2014 Feb;20(1):51-7 YanPing Zhang, Jitesh D Kawedia, Alan L Myers, Chelsey M McIntyre, Peter M Anderson, Mark A Kramer, Kirk S Culotta[4]

The study included solutions of 1:1 Ifosfamide and Mesna at final concentrations of 10, 20 and 30 mg/mL prepared in 0.9% Sodium Chloride (in PVC bags). Solutions were stored at room temperature. Concentrations of Ifosfamide and Mesna were measured over 14 days using a stability-indicating reversed phase high-performance liquid chromatography (HPLC) assay with ultraviolet detection. The study concluded that Ifosfamide and Mesna were both physico-chemically stable (>94%) for 14 days in all tested infusion solutions (10, 20 and 30 mg/mL), however this is not within the BP specification (95 – 105%) and also did not include analysis of degradation products.

Stability of Ifosfamide in Solutions for Multiday Infusion by External Pump, Anticancer Drugs. 1995 Aug;6(4):604-7, L Leone, A Comandone, C Oliva, P Bussi, F Goffredo, S Bretti, C Bumma[5]

The stability of Ifosfamide in Ringer lactate buffer solution either alone or mixed with Mesna at 37°C for a 7-day period was analysed by HPLC, Loss of active did not exceed 3.2% at day 7, however, degradation products were not examined.

Assessment carried out and report written by

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References

1. A Standard Protocol for Deriving and Assessment of Stability Part 1 – Aseptic Preparations (Small molecules) Edition 5, September 2019 (NHS PQA Committee)
2. Baxter internal stability study of Ifosfamide (reference: SB/STABR/17/003) and Ifosfamide in combination with Mesna (reference SB/STABR/17/009) viewed under a confidentiality agreement
3. Personal communication received from Baxter received 15/05/2020
4. Physical and Chemical Stability of High-Dose Ifosfamide and Mesna for Prolonged 14-day Continuous Infusion, J Oncol Pharm Pract 2014 Feb;20(1):51-7 YanPing Zhang, Jitesh D Kawedia, Alan L Myers, Chelsey M McIntyre, Peter M Anderson, Mark A Kramer, Kirk S Culotta
5. Stability of Ifosfamide in Solutions for Multiday Infusion by External Pump, Anticancer Drugs. 1995 Aug;6(4):604-7, L Leone, A Comandone, C Oliva, P Bussi, F Goffredo, S Bretti, C Bumma