

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 products¹.

Drug: Mitoxantrone

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

3 days at up to 0.5mg/ml stored in a refrigerator at 2 – 8°C in Sodium Chloride 0.9%

British Pharmacopoeia specification for product.

BP2020 has a monograph for Mitoxantrone Infusion defined as a sterile solution containing Mitoxantrone Hydrochloride. It is prepared by diluting Sterile Mitoxantrone Concentrate with a suitable diluent in accordance with the manufacturer's instructions. Also for Sterile Mitoxantrone Concentrate defined as a sterile solution of Mitoxantrone Hydrochloride in Water for Injections.

Sterile Mitoxantrone Concentrate

Content of mitoxantrone - 90.0 to 105.0% of the stated amount.

Related substances

Impurity D < 3.0%

Unassigned related substances < 1.0% each < 5.0% overall

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
Accord Healthcare PL 20075/0412	Chemical and physical stability of the diluted product has been demonstrated for a period of 7 days or 14 days at 15-25°C and 2-8 °C respectively in partially used vials. (see comment below)	2 mg/ml concentrate for solution for infusion. Sodium chloride, Sodium acetate, Acetic acid, Water for Injections.	Study provided covered 0.1 - 0.6mg/ml for 84 days at 2-8°C and 20 – 25°C. No replicates, no degradation product analysis, no sub-visible particle counts carried out. ²	Sufficient data supplied to support at least 72 hours (recommended refrigeration at 2 – 8°C) after dilution	Product is likely to be stable for much longer but see comments regarding limitations of studies.
Baxter Healthcare Ltd PL 00116/0398	8 hours after dilution	2 mg/ml concentrate for solution for infusion. Sodium chloride, Sodium acetate, Acetic acid, Water for Injections.	Retrospectively a stability statement was provided which referred to a 63 day study 0.02 - 2mg/ml. Includes degradation product analysis which remain within limits but no sub-visible particle counts. No raw data provided but overall judged enough to support the required 3 days shelf life assignment. ³	Sufficient data supplied to support at least 72 hours (recommended refrigeration at 2 – 8°C) after dilution	Product is likely to be stable for much longer but see comments regarding limitations of studies.

Manufacturer	SmPC shelf life	Excipients / formulation details	Assessment of Extended studies submitted	Shelf-life recommendation (section 10 units)	Comments on further shelf life extension
Pfizer (Hospira UK Ltd)	Chemical and physical stability of the diluted product has been demonstrated for 72 hours when stored at room temperature.	2 mg/ml concentrate for solution for infusion. Glacial acetic acid Sodium acetate Sodium chloride Sodium metabisulfite Water for Injections	N/A	SmPC shelf life 72 hours (recommended refrigeration at 2 – 8°C)	Product is likely to be stable for much longer but see comments regarding limitations of studies.

Conclusions (based on the data provided)

The Accord SmPC covers up to 14 days refrigerated for the diluted solution but also states in partially used vials, this is somewhat contradictory. The stability study submitted with the tender covered 84 days storage in the refrigerator (2 – 8°C) and at room temperature at 0.1 and 0.6mg/ml in Sodium Chloride 0.9%, loss of active drug remained less than 5% throughout, stability was better on the refrigerated samples. The study was limited as listed above but does provide evidence that the drug is relatively stable when diluted within this range.

The Baxter SmPC provides only eight hours shelf-life, the additional paper covered 0.02 and 2mg/ml over 63 days at 2 – 8°C plus 2 days at 25°C. Analysis was by visual inspection, pH, assay for active drug and degradation products (impurities A and D) and all results stayed within limits after the 65 days analysis. Intermediate analysis was carried out but not reported / discussed in the summary.

The Pfizer (Hospira) product has 72 hours within the SmPC and no further data was supplied. The formulations are essentially similar for the three brands although the Pfizer (Hospira) also contains Sodium Metabisulfite as an anti-oxidant, the Baxter product is stated as filled under Nitrogen in the SmPC. The shelf life of 72 hours at 2 – 8°C diluted in Sodium Chloride 0.9% or Dextrose 5% can be assigned to all three products. There is data to support that the drug is stable for longer but the quality of the studies / study report means that this should be applied conservatively (see also below).

Published and other relevant reports

The stability of carboplatin, diamorphine, 5-fluorouracil and mitoxantrone infusions in an ambulatory pump under storage and prolonged “in use” conditions. J Clin Pharm Ther; 16: 123-129. 1991, Northcott M, Allsopp MA, Powell H, Sewell GJ.⁴

The study looked at storage at 4°C and also at 37°C for Mitoxantrone at 2mg/ml and showed little evidence of degradation although looked at loss of active drug only.

In house studies

Reports from an in-house study conducted at the Torbay Regional Quality Control laboratory assigned a shelf life of 49 days refrigerated (no degradation seen) and 49 days at room temperature (slight degradation seen) at 0.2mg/ml in Sodium Chloride 0.9% in syringes (part referenced in the article⁵), a further study undertaken in Plymouth looked at 0.1mg/ml in Sodium Chloride 0.9% in polyolefin and glass containers and assigned 42 days shelf life at 2 – 8°C and at room temperature. Neither study was carried out to today’s standards and both were based on loss of active only. There is also data listed on Stabilis from Ebewe Pharma which lacks detail but does cover a range on concentrations, diluents and storage conditions and implies stability for 7 to 28 days⁶.

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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. Physical & Chemical In-use Stability of Mitoxantron 2mg/ml Concentrate for solution for infusion (Accord) (25/06/2015)
3. Baxter stability data proforma (for tender use Wave 12) (no other references included)
4. The stability of carboplatin, diamorphine, 5-fluorouracil and mitoxantrone infusions in an ambulatory pump under storage and prolonged “in use” conditions. J Clin Pharm Ther; 16: 123-129. 1991, Northcott M, Allsopp MA, Powell H, Sewell GJ.
5. Pharmaceutical aspects of home infusion therapy for cancer patients, Pharm J; 238: 476-478. 1987, Adams PS, Haines-Hutt RF, Bradford E, Palmer A, Rowland CG.
6. Stabilis <https://www.stabilis.org/> accessed 8th June 2020