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: **Cytarabine**

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

7 days at 2 – 8°C in Sodium Chloride 0.9% at up to 25mg/ml

7 days at room temperature at 20 – 100mg/ml in a syringe

British Pharmacopoeia specification for product. General BP requirements (e.g. Parenteral Preparations Monograph) also apply

Monograph - Cytarabine Injection - Cytarabine Injection is a sterile solution of Cytarabine in Water for Injections. (Ready to use injection)

Content of cytarabine - 95.0 to 105.0% of the stated amount.
Related substances
- Uracil arabinoside <2.0%
- Unspecified Impurities <0.5%

Monograph - Cytarabine for Injection - Cytarabine for Injection is a sterile material consisting of Cytarabine with or without excipients (Powder for reconstitution)

Content of cytarabine - 95.0 to 105.0% of the stated amount.
Related substances
- Uracil arabinoside <1.0%
- Unspecified Impurities <0.5%

The Cytarabine Injection (Ready to use Injection) monograph is the most relevant for this specification

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 20075/0121	Chemical and physical in-use stability has been demonstrated in sodium chloride injection (0.9 % w/v) and dextrose injection (5% w/v) for up to 24 hours at temperature below 25° C and for up to 72 hours at 2-8° C .	100 mg/ml Solution for Injection Macrogol 400 Trometamol (For pH adjustment) Water for Injections	Study report provided covering 0.19 - 7.6mg/ml for 84 days and 100mg/ml in syringe for 60 days. No replicates, lack of data points (only 3 for syringes) presentation of results is extremely poor., No statistical analysis of data.[2]	Despite the limitations the study is sufficient to assign a shelf life of 7 days as a concentrate in syringes or diluted in Sodium Chloride 0.9%	See below
Fresenius Kabi PL 18727/0024	After dilution, chemical and physical in-use stability has been demonstrated for 8 days below 25°C.	100 mg/ml solution for injection Hydrochloric acid (for pH adjustment) Sodium hydroxide (for pH adjustment) Water for injections	N/A	SmPC supports 7 days below 25°C.	SmPC supports 8 days below 25°C.
Pfizer (Hospira UK Ltd) PL 04515/0057	In use: Chemical and physical in-use stability has been demonstrated for 7 days at room temperature.	100mg/ml injection Water for Injections Hydrochloric Acid (for pH adjustment) Sodium Hydroxide (for pH adjustment)	N/A	SmPC supports 7 days below 25°C	SmPC supports 7 days below 25°C
Pfizer (Hospira UK Ltd) PL 04515/0040	Chemical and physical in-use stability has been demonstrated for 7 days at room temperature.	20mg/ml solution for infusion Hydrochloric Acid Sodium Hydroxide Water for injections Sodium Chloride	N/A	SmPC supports 7 days below 25°C	SmPC supports 7 days below 25°C

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 (own livery) (included for clarity) PL 00057/0954	Use immediately	20mg/ml solution for infusion Hydrochloric Acid Sodium Hydroxide Water for injections Sodium Chloride	N/A	See below	See below
Pfizer (own livery) (included for clarity) PL 00057/0955	Use Immediately	100mg/ml solution for infusion Hydrochloric Acid Sodium Hydroxide Water for injections	N/A	See below	See below

Conclusions (based on the data supplied)

The Accord study was poorly presented but does cover an extended period and the drug did look stable diluted in saline for the whole 84 days study period. It did degrade rapidly in Dextrose 5% and was out of specification (>5% loss) at day 14 in this diluent, fungal growth was also seen in one sample. At 100mg/ml in a syringe the drug also looked relatively stable but the study was aborted after 60 days due to fungal growth in the syringe. The Fresenius Kabi and Pfizer (Hospira) preparations have a statement in the SmPC to cover seven days shelf life. Pfizer also has licences for Cytarabine in its own livery which has a use immediately stability statement, however, the formulation appears identical to the Hospira liveried product and hence it would be safe to extrapolate to cover this product range if necessary. It does need to be clear in local stability assessments as to which product licence numbers are being used.

Refrigerated storage should not be an issue for lower concentrations although for the more concentrated solutions there have been reported problems with precipitation reflected in the requirement in some SmPCs to warm solutions for injection prior to handling. The 100mg/ml concentration is at the solubility limit for cytarabine[3] hence at or close to this concentration room temperature storage is recommended.

Published and other studies

None found of suitable repute to add to the information above.

Assessment carried out and report written by

Mark Santillo, Regional Quality Assurance Officer, South West England
Chair of the NHS Pharmaceutical Research and Development Group. 11th November 2020

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 and Chemical In-use stability of Cytarabine 100mg/ml Concentrate for Solution for Infusion (Accord), 30 May 2014
3. Martindale The Extra Pharmacopoeia
   SmPCs sent as part of the tender in July 2019 or accessed on line August 2020