

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: **Bendamustine**

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

Up to 0.6mg/ml in Sodium Chloride 0.9% 48 hours at 2 – 8°C in infusion bags (non-PVC)

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

No BP Monograph for injection or active substance

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	After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 °C and 2 days at 2 °C to 8 °C in polyethylene bags.	Mannitol	N/A	3.5 hours at 25 °C or 2 days at 2 °C to 8 °C in polyethylene bags	Not possible

Manufacturer	SmPC shelf life	Excipients / formulation details	Assessment of Extended studies submitted	Shelf-life recommendation (section 10 units)	Comments on further shelf life extension
Consilient	Generic SmPC submitted without the MIA Holder completed: After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25°C/ 60% RH and 2 days at 2°C to 8°C in polyethylene bags.	Mannitol	N/A	3.5 hours at 25 °C or 2 days at 2 °C to 8 °C in polyethylene bags	Not possible
Kent	Chemical and physical in-use stability (diluted solution) has been demonstrated for 3.5 hours at 25°C/ 60% RH and 2 days at 2°C to 8°C in polyethylene bags.	Mannitol	N/A	3.5 hours at 25 °C or 2 days at 2 °C to 8 °C in polyethylene bags	Not possible
Seacross	After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25°C/ 60% RH and 2 days at 2°C to 8°C in polypropylene bags.	Mannitol Hydrochloric acid (pH adjustment)	N/A	3.5 hours at 25 °C or 2 days at 2 °C to 8 °C in polyethylene bags	Not possible
Dr. Reddys (Synthon Hispania)	After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25°C/ 60% RH and 2 days at 2°C to 8°C in polyethylene bags.	Mannitol	Further study submitted which showed at 48 hours at 2 – 8°C in 0.9% NaCl in polyethylene bags only 92.7% remains (this is within SmPC) 72 hours data is well out of spec for degradation products, also out of spec after 8 hours at room temperature.	3.5 hours at 25 °C or 2 days at 2 °C to 8 °C in polyethylene bags	Not possible

Manufacturer	SmPC shelf life	Excipients / formulation details	Assessment of Extended studies submitted	Shelf-life recommendation (section 10 units)	Comments on further shelf life extension
Fresenius Kabi	After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25°C/ 60% RH and 2 days at 2°C to 8°C in polyethylene bags.	Mannitol	N/A	3.5 hours at 25 °C or 2 days at 2 °C to 8 °C in polyethylene bags	Not possible
medac	After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 °C/60 % RH and 2 days at 2 °C to 8 °C in polyethylene bags.	Mannitol	N/A	3.5 hours at 25 °C or 2 days at 2 °C to 8 °C in polyethylene bags	Not possible
Zentiva	After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25°C/60% RH and 2 days at 2°C to 8°C in polyethylene bags	Mannitol	N/A	3.5 hours at 25 °C or 2 days at 2 °C to 8 °C in polyethylene bags	Not possible

Conclusions

All of the products available are based on EMA generic product specifications and SmPCs and ready to administer presentations can be assigned a shelf life of 3.5 hours at 25 °C or 2 days at 2 °C to 8 °C in polyethylene bags of 0.9% Sodium Chloride. Data supplied by Dr Reddy's indicates that this is the maximum shelf life that is possible to assign.

Published studies

There are a couple of published studies but they do not add anything further to this assessment.

Assessment carried out and report written by

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Chair of the NHS Pharmaceutical Research and Development Group. 27th May 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. Bendamustine lyo reconstitution and dilution stability protocol and report (Dr Reddy's), Quinta no. SSP-A-SYN-BUS-lyo-001-16.03
SmPCs accessed on-line or sent as part of the tender between June and October 2019