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: **Etoposide**

Note that this assessment does not cover the Etoposide Phosphate product.

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

4 days at 0.19 - 0.36 mg/ml at room temperature in an infusion bag

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

BP2020 monograph for Etoposide Infusion - Etoposide Infusion is a sterile solution containing Etoposide. It is prepared by diluting Sterile Etoposide Concentrate with a suitable diluent in accordance with the manufacturer's instructions.

Content of etoposide 95.0 to 105.0% of the stated amount.
Related substances
cis-etoposide <2.0%

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 20075/0376	Chemical and physical in-use stability of the solution diluted to a concentration of 0.2 mg/ml and 0.4 mg/ml has been demonstrated in sodium chloride injection (0.9 % w/v) and glucose injection (5% w/v) for up to 96 hours and 48 hours at temperature 20°- 25° C respectively.	20 mg/ml Concentrate for Solution for Infusion Citric acid, anhydrous Benzyl alcohol Polysorbate 80 Macrogol 300 Ethanol, anhydrous	Study replicates in 250ml and 500ml bags, 0.20 - 0.40mg/ml (plus 0.45mg/ml which is non-compliant at the first data point). Some precipitation at day 4 at 0.4mg/ml. Chemical stability OK at 28 days at 0.2mg/ml. No replicates (apart from different size bags) no degradant analysis, no sub-visible particle counts (this is an important indicator for etoposide)[2]	Study does not add anything to SmPC. Suggested shelf life up to 2 days at up to 0.4mg/ml (normally recommend 0.36mg/ml maximum conc.) 4 days can be assigned for lower concentrations at room temperature	Etoposide is chemically quite stable in dilute solution; however, shelf life is limited by physical stability with precipitation increasing over time
Fresenius Kabi PL 18727/0029	Chemical and physical in-use stability of the solution diluted to a concentration of 0.2 mg/ml or 0.4 mg/ml has been demonstrated up to 24 hours at 15°C to 25°C.	20 mg/ml concentrate for solution for infusion Macrogol 300 Polysorbate 80 Benzyl alcohol Ethanol Anhydrous citric acid	N/A	SmPC suggests shelf life of up to 24 hours at up to 0.4mg/ml (normally recommend 0.36mg/ml maximum conc.)	SmPC suggests shelf life of up to 24 hours at up to 0.4mg/ml

Manufacturer	SmPC shelf life	Excipients / formulation details	Assessment of Extended studies submitted	Shelf-life recommendation (section 10 units)	Comments on further shelf life extension
Medac PL 11587/0096	The diluted product (0.2 mg/ml) should be used immediately. The physical and chemical in-use stability of the diluted product (0.4 mg/ml) has been demonstrated for 24 hours at 25 °C.	20 mg/ml concentrate for solution for infusion Citric acid (anhydrous) Polysorbate 80 Macrogol 300 Ethanol	Additional statement provided (but no supporting data) for 5 days shelf life at 0.1 and 0.2mg/ml at room temperature[3]	Suggested shelf life up to 24 hours at up to 0.4mg/ml (normally recommend 0.36mg/ml maximum conc.) 5 days can be assigned for lower concentrations (0.1 – 0.2mg/ml) at room temperature	Suggested shelf life up to 24 hours at up to 0.4mg/ml up to 5 days can be assigned for lower concentrations. Shelf life is limited by physical stability with precipitation increasing over time

Conclusions (based on the data provided)

The statement in the SmPC from Accord is somewhat ambiguous, clarification was received from Accord[4] which stated that at 0.2mg/ml a shelf life of 96 hours could be applied in both Sodium Chloride 0.9% and Dextrose 5% and 48 hours could be applied at 0.4mg/ml in either diluent. Chemically Etoposide is relatively stable with the Accord paper showing good stability (based on loss of active only) for up to 28 days at room temperature in either Sodium Chloride 0.9% or Dextrose 5%. The shelf life for diluted solutions is limited by the risk of precipitation which increase over time and as concentration is increased (within the clinically used concentration range). Due to the complexity of the formulation and the risk of precipitation extrapolation between brands is not recommended. Label to check for particles before use and not use if particles are present.

Published and other relevant reports

Physicochemical stability of etoposide diluted at range concentrations between 0.38 and 1.75 mg/mL in polyolefin bags, EJHP 2018, D'Huart E, Vigneron J, Lider P, Demoré B.[5]

This study looked at the stability of etoposide solutions (Mylan) between 0.38 and 1.75 mg/mL, diluted in Sodium Chloride 0.9% and in Dextrose 5% in polyolefin bags, stored at 25°C and between 2°C to 8°C. Chemical stability was evaluated by HPLC and physical stability by visual examination and sub-visible particle counting. The conclusion recommended storage at 25°C and Dextrose 5% as diluent for etoposide high concentrations with 61-day stability

up to a concentration of 1.26 mg/mL and 28-day stability up to a concentration of 1.75 mg/mL. The paper also recommends the use of an administration set with an in-line micro-filter and that storage at 2°C to 8°C and the use of 0.9% NaCl increase the risk of precipitation. Although this study was robustly carried out it is recommended that some caution is needed if you plan to use higher concentrations of etoposide, of course with higher concentrations then the solubilising agents are also in higher concentration and may help to keep the drug in solution.

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. Physical and Chemical Stability of Etoposide 20mg/ml Concentrate for solution for Injection (Accord) (21/07/2015)
3. Etoposide 20mg/ml - In-use stability of product (Medac) December 4, 2018
4. Personal communication received from Accord 19th June 2020 reference AUK20-003135
5. Physicochemical stability of etoposide diluted at range concentrations between 0.38 and 1.75 mg/mL in polyolefin bags, EJHP 2018, D'Huart E, Vigneron J, Lider P, Demoré B.