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: **Dacarbazine**

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

24 hours at up to 2mg/ml stored in a refrigerator at 2 – 8°C in Sodium Chloride 0.9% infusion bag

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

BP 2020 monograph for dacarbazine Injection defines as a sterile solution of Dacarbazine in Water for Injections. It is prepared by dissolving Dacarbazine for Injection in the requisite amount of Water for Injections.

Dacarbazine for Injection is a sterile material consisting of Dacarbazine with or without excipients.
Content of dacarbazine - 90.0 to 110.0% of the stated amount.
5-aminoimidazole-4-carboxamide hydrochloride < 0.6%
Related substances
First secondary peak < 1.0%
Other secondary peaks < 0.5%
Sum of secondary peaks < 3.0%

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
Medac PL 11587/0008 PL 11587/0009 PL 11587/0010 PL 11587/0011	For the reconstituted solution chemical and physical in-use stability has been demonstrated for 24 hours at 20 °C protected from light. The reconstituted and further diluted solution must be used immediately	Powder for solution for infusion. Citric acid, anhydrous, Mannitol	Some additional data supplied which supports 24 hours for the diluted solution.[2]	The diluted product can be assigned a shelf life of up to 24 hours stored under light protection in a refrigerator (+2°C to +8°C). See below.	Shelf-life extension beyond 24 hours should not be considered.

Conclusions (based on the data provided)

Stability statement supplied states 'The further diluted solution has a physical-chemical stability of 8 hours if stored at room temperature, protected from light, and of 24 hours if either the concentration is 4.0 mg/mL stored under light protection or if a solution is stored under light protection in a refrigerator (+2°C to +8°C)'. the paper further states that 'Dacarbazine is extremely sensitive to light exposure. Preparation and administration should be performed only if protected from light. During administration, the infusion container and administration set should be protected from exposure to daylight.' Furthermore, degradation products, which could possibly appear, are under the suspicion to cause, even if in slight concentration, a higher toxicity of the drug.

Overall although a shelf life of 24 hours for refrigerator stored product can be supported it is best to keep shelf life of diluted Dacarbazine injection as short as possible to minimise any risks from toxicity enhancing degradation products.

Published and other relevant reports

Compatibility of plastics with cytotoxic drug solutions - comparison of polyethylene with other container materials, Int J Pharm ; 185: 113-121. 1999, Beitz C, Bertsch T, Hannak D, Schrammel W, Einberger C, Wehling M.[3]

This paper was more focused on container compatibility but did include HPLC analysis for the active substance. It looked at Dacarbazine 0.64mg/ml and suggested a shelf life of 48 hours, however, degradation products were detected but not quantified. This paper should not be used to further extend the product shelf life.

Stability of dacarbazine in amber glass vials and polyvinyl chloride bags, Am J Health-Syst Pharm ; 59: 1351-1356. 2002, El Aatmani M, Poujol S, Astre C, Malosse F, Pinguet F.[4]

The paper looked at the stability of 1.4mg/ml Dacarbazine for up to seven days stored in a refrigerator (2 – 8°C) and at room temperature, it did include analysis of the degradation products including 2-Azahypoxanthine. The paper does accept up to 10% loss of active which, although the BP monograph allows 90% of stated content, is not acceptable for a drug which produces potentially toxicity enhancing degradation products.

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. Dacarbazine 100 mg (-200 mg-, -500 mg-, -1000 mg-) medac Guidelines for the Safe Handling and Drug Stability Information, August 2011
3. Compatibility of plastics with cytotoxic drug solutions - comparison of polyethylene with other container materials, Int J Pharm ; 185: 113-121. 1999, Beitz C, Bertsch T, Hannak D, Schrammel W, Einberger C, Wehling M.
4. Stability of dacarbazine in amber glass vials and polyvinyl chloride bags, Am J Health-Syst Pharm ; 59: 1351-1356. 2002, El Aatmani M, Poujol S, Astre C, Malosse F, Pinguet F.