Background

As part of a review of stability data for cytotoxic drugs, 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: **Treosulfan Injection**

NHS requirements for shelf life / preparations prepared

50mg/ml reconstituted solution for infusion or further diluted in sodium chloride 0.9% (or dextrose 5% see below)

British Pharmacopoeia specification for product.

The BP2020 has no monograph for Treosulfan injection or indeed for the API starting material

Assessment:

Manufacturer	SmPC shelf life	Excipients / formulation details	Other comments	Shelf-life recommendation
Medac (Trecondi) EU/1/18/1351/001 EU/1/18/1351/002 EU/1/18/1351/003 EU/1/18/1351/004	After reconstitution with sodium chloride 4.5 mg/mL (0.45%) solution, chemical and physical stability has been demonstrated for 2 days at 25 °C. **Do not** store in a refrigerator (2 °C-8 °C) as this might cause precipitation	No excipients Note for reconstitution with 0.45% sodium chloride (see below)	Additional information from Medac[2]. After reconstitution to a concentration of 50 mg/mL, chemical and physical stability has been demonstrated for up to 3 days at 25 °C.	After reconstitution with 0.45% sodium chloride to a concentration of 50 mg/mL, shelf life of up to 3 days at 25 °C can be assigned.
Medac (Generic) PL 11587/0002	The prepared solutions should be used immediately. **Do not** store the reconstituted or the diluted product in a refrigerator (2 – 8 °C) as this might cause precipitation.	No excipients. Treosulfan is used for intravenous infusion after being dissolved in 100 mL of water for injections.	Additional information from Medac[3]. At room temperature reconstituted Treosulfan (50mg/ml) is physico-chemically stable for four days. Also, if diluted in Sodium chloride 0.9% or Glucose 5% to 20mg/ml.	After reconstitution to a concentration of 50 mg/mL, or when diluted to 20mg/ml in Sodium Chloride 0.9% or Dextrose 5% shelf life up to 4 days at 25 °C can be assigned.
Tillomed PL 11311/0572	Chemical and physical in-use stability has been demonstrated for 12 hours at 30°C. **Do not** store the reconstituted product in a refrigerator (2 - 8°C) as this might cause precipitation.	No excipients. Treosulfan is used for intravenous infusion after being dissolved in 100 mL of water for injections.	See below	See below: After reconstitution to a concentration of 50 mg/mL, or when diluted to 20mg/ml in Sodium Chloride 0.9% or Dextrose 5% shelf life up to 4 days at 25 °C can be assigned.

Conclusions (based on the data above)

Treosulfan (Trecondi – Medac) should be reconstituted with 0.45% sodium chloride injection (or a 50:50 mixture of sodium chloride 0.9% and water for Injection), this was a requirement of licensing due to the osmolarity, which can have an impact on tolerability in paediatric patients. In the context of the PIP (Paediatric Investigation Plan), the EMA (European Medicines Agency) required the use of 0.45% sodium chloride as mandatory for the approval in the treatment of children[4]. The additional stability data supplied[2] showed that the drug was stable over the 72-hour period tested although the pH did drop substantially during this time so it is recommended that this time is not exceeded.

Medac also provided data for the generic Treosulfan[4] which supported a shelf life of up to four days at room temperature when used as the reconstituted solution (in water for injection) or further diluted in sodium chloride 0.9% or dextrose 5% to 20mg/ml. This was in relation to the concentration of active which remained fairly stable throughout the total 7 days study period. The pH did decrease significantly from day 0 to day 7, although the pH decrease was seen immediately when the solution was diluted in both sodium chloride 0.9% and glucose 5% in PVC and PE bags (the decrease was slower in glass containers but reached a similar end point). Due to the significant change in pH it is advised to keep to the suggested four days shelf life at room temperature.

The Tillomed SmPC only includes data for up to 12 hours at 30^0C, however, all three products are identical in formulation, being the pure drug without excipients and hence the above data can safely be extrapolated to include the Tillomed product.

Summary

For paediatric use Trecondi should be reconstituted with 0.45% sodium chloride to a concentration of 50 mg/mL, and can be assigned a shelf life of up to 3 days at 25 °C. For adult use either of the generic products listed can be reconstituted with water for injection to 50mg/ml and can be assigned a shelf life of up to 4 days at 25 °C. The reconstituted products can also be further diluted with sodium chloride 0.9% or dextrose 5% and be assigned a shelf life of up to 4 days at 25 °C, at concentrations between 20mg/ml and 50mg/ml.

Published Studies

There is one published study listed on Stabilis[5] but this is not freely available in the UK and would appear not to meet with the NHS standards[1] (allowed 10% degradation and did not include visual inspection, also results showed a high degree of variation). Hence this does not change the advice above.

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. Trecondi® 1000 / 5000 mg Powder for solution for infusion Details about Handling and Stability, June 2020
3. Treosulfan Injection Details about Handling and Stability, August 2008
4. Information received from Medac 14/01/21
5. Treosulfan : chemisch-physikalische stabilität, Hinweise für die pharmazeutisch-onkologische praxis: Krankenhauspharmazie ; 11: 576-580. 2000: Hilger RA, Kredtke S, Barth J. SmPCs accessed on-line 20/01/2021