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: **Epirubicin solution for injection**

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

7 days at 2 – 8$^{O}$C at 2mg/ml in a syringe

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

BP 2020 monograph exists for Epirubicin injection

- Content of Epirubicin hydrochloride - limits 95.0 to 110.0% of the stated amount
- Related substances
  - Impurities A (Doxorubicinone) < 2.0%
  - Impurity C (Doxorubicin) < 1.0%
  - other secondary peaks < 0.5%
  - sum of all secondary peaks. < 4.0%
- pH

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<br><br>PL 20075/0024 | If not used immediately, in use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. | Sodium chloride and pH adjustment | Extended data 0.1 - 2mg/ml in polyolefin bags and syringes for 84 days (96 days for syringes). Poor data presentation. Not compliant with YCD, no replicates, no sub-visible particles, no degradation products[2] | Satisfactory for seven days shelf life assignment at 0.1 - 2mg/ml in polyolefin bags and syringes | Study is for an extended period but data is not well presented and study non-compliant with YCD |
| Hikma (Consilient)<br><br>Draft SmPC only | Chemical and physical stability was demonstrated, after dilution in Sodium Chloride 0.9% or Glucose 5% solution, for 72 hours when stored in a refrigerator. | Sodium lactate 50% Sodium chloride and pH adjustment | None submitted | 72 hours when stored in a refrigerator | Formulation is different from other suppliers and therefore data cannot be extrapolated |
| Medac<br><br>PL 11587/0043 | Epirubicin hydrochloride may be further diluted, under aseptic conditions, in glucose 5 % solution or sodium chloride 0.9 % solution and administered as an intravenous infusion. The chemical and physical in-use stability has been demonstrated for 48 hours at 25°C in the absence of light. | Sodium chloride and pH adjustment | Additional statement provided covering up to 100 days in syringes and 84 days in bags but no data was provided to support this.[3] | Satisfactory for seven days shelf life assignment at 0.1 - 2mg/ml in polyolefin bags and syringes | Statement only supplied although for an extended period |

| 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<br><br>PL 00057/1023 | From a microbiological point of view, the product should be used immediately after first penetration of the rubber stopper. If not used immediately, in use storage times and conditions are the responsibility of the user | Sodium chloride and pH adjustment | Additional statement supplied on request covering concentrations of 0.04 and 0.1mg/mL, in 0.9% (w/v) sodium chloride solution or 5% (w/v) glucose solution, and packaged in either polypropylene or polyvinylchloride containers:<br>14 days at 5°C, 12 days at 25°C shelf life but no supporting data supplied and study is clearly quite historical[4] | Satisfactory for seven days shelf life assignment at 0.1 - 2mg/ml in polyolefin bags and syringes | Statement only supplied |

Conclusions (based on the data supplied)

The Accord, Medac and Pfizer products have an identical formulation; that for Hikma is different (containing sodium lactate). None of the stability studies supplied comply with the NHS standards but the data is sufficient to assign a shelf life of 7 days stored in a refrigerator in syringes and polyolefin bags for the Accord, Medac and Pfizer brands, the shelf life for the Hikma (Consilient) product should be restricted to 72 hours stored in the refrigerator. In terms of beyond this, the drug itself does appear to be reasonably stable but there is no indication that the studies have looked at degradation products which do have limits in the BP. The studies reported below do give further data to support extended shelf life assignment.

Published studies

Studies on the stability and compatibility of cytotoxic drug infusion with the Tevadaptor system, EJOP; 8, 3: 26-30. 2014, Sewell G, Massimini M.[5]

The study is mainly focussed around the compatibility with the Tevadaptor device and is light on the detail of the results obtained, only reporting the initial and final data points. Nevertheless, this covers Epirubicin (Fresenius Kabi) undiluted in BD syringes with and without the Tevadaptor and indicates good stability in terms of loss of active, pH, appearance and sub-visible particle counts after 84 days in the refrigerator at 2-8$^{o}$C protected from light.

Stability of intravesical epirubicin infusion: a sequential temperature study. J Clin Pharm Ther ; 28: 349-353. 2003, Sewell GJ, Rigby-Jones AE, Priston MJ.[6]

Epirubicin instillation (1mg/mL) in polypropylene syringes was sequential incubated for 84 days at 8°C followed by 2h at 25°C and 1h at 37°C, the latter two temperatures replicating transport and intravesical conditions, respectively. The instillation was both chemically and physically stable under those incubation conditions (no degradation). The formulation of epirubicin (liquid vs rapid dissolution powder) used to prepare the instillation infusions did not affect stability.

Epirubicin stability in syringes and glass vials and evaluation of chemical contamination. Can J Hosp Pharm ; 43: 265-272. 1990, Walker SE, Lau DWC, DeAngelis C, Lazetta J, Coons C.[7]

Study carried out at 1mg/ml and undiluted in syringes for 150 days refrigerated and at room temperature

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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 Diluted Solutions and Hold Time study of Epirubicin Hydrochloride 2mg/ml Concentrate for Solution for Infusion (27/02/2014)
3. Epirubicin hydrochloride 2 mg/ml solution for injection Details about Handling and Stability (Medac) Version: 04 September 2016
4. Pharmorubicin (epirubicin) Stability After Further Dilution, Pfizer European Medical Information Created on 28AUG 2012
5. Studies on the stability and compatibility of cytotoxic drug infusion with the Tevadaptor system, EJOP; 8, 3: 26-30. 2014, Sewell G, Massimini M.
6. Stability of intravesical epirubicin infusion: a sequential temperature study. J Clin Pharm Ther ; 28: 349-353. 2003, Sewell GJ, Rigby-Jones AE, Priston MJ.
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