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: **Fludarabine Phosphate injection**

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

7 days at up to 1.2mg/ml solution stored in a refrigerator (2 – 8°C) in Sodium Chloride 0.9% infusion

7 days at up to 12mg/ml solution stored in a refrigerator (2 – 8°C) in a syringe

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

BP 2020 has a monograph for Fludarabine Phosphate (starting material) only no monograph for the injection

Related substances

Impurity A *<0.8 %*

Impurity C *<0.4 %*

Impurity B *<0.2 %*

Unspecified impurities eluting before fludarabine phosphate <0.10%

Impurity E *<0.2 %*

Impurity F *<0.2 %*

Impurity D *<0.15 %*

Unspecified impurities eluting after fludarabine phosphate <0.10%

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 20075/0379	Chemical and physical in-use stability has been demonstrated at 0.2 mg/ml & 6.0 mg/ml after dilution with 0.9% Sodium chloride and 5% Glucose Injection for 7 days at 2-8 °C and 5 days at 20 – 25 °C in non-PVC bags and Glass bottles.	25 mg/ml Concentrate for Solution for Injection or Infusion. Mannitol Disodium hydrogen phosphate dihydrate. Water for Injection	N/A	Between 0.2 - 6.0 mg/ml after dilution with 0.9% Sodium chloride or 5% Glucose Injection shelf life 7 days at 2-8 °C (or 5 days at 20 – 25 °C) in non-PVC bags (see also below)	
Teva UK Limited PL 00289/0938	Chemical and physical in-use stability of the solution prepared for injection or infusion has been Demonstrated as: 0.3 – 6.0mg/ml in Sodium Chloride 0.9% or Dextrose 5% in a non-PVC infusion bag 5 days in a refrigerator (2 – 8°C) or at ambient temperature / light.	25mg/ml Concentrate for Solution for Injection or Infusion Mannitol Sodium hydroxide (for pH adjustment) Water for Injections	Study 0.25 - 6mg/ml in polyolefin bag or syringe/ Not enough data points (only 2 post T=0). Marked as an interim report although it is dates Jan 2013. No sub-visible particles, degradation products no replicates[2]	Between 0.3 - 6.0 mg/ml after dilution with 0.9% Sodium chloride or 5% Glucose Injection shelf life 5 days at 2-8 °C (or at 20 – 25 °C) in non-PVC bags or syringes.	

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 PL 0142/1013	The physicochemical stability of the drug product after reconstitution in water for injections has been demonstrated for 8 hours at 25°C and for 7 days at 2-8°C.	Powder for Solution for Injection or Infusion Mannitol Sodium hydroxide (for pH adjustment)	N/A	See below	

Conclusions (based on the data provided)

Formulations for the two products appear similar (although with different pH adjustment). The Teva paper submitted was only the interim report and included days 0, 7 and 14 but not the day 28 data which was planned, it is not clear why the report from 2013 wasn't updated with the final data point. The data submitted based on loss of active only (sub-visible particle counts were planned at day 28), they do indicate reasonably good stability based on the limited data set. The data can be used to extrapolate the Teva SmPC data into syringes, and it would also be reasonable to apply the extrapolation to the Accord product.

Fludarabine Phosphate is also available as a lyophilised powder presentation, according to the Accord SmPC the pH of the reconstituted solution is slightly above that of the solution for injection, however, the SmPC does have seven days stability for the reconstituted solution and it would therefore seem reasonable to extrapolate the diluted stability from the other products.

Published and other relevant reports

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

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 Fludarabine (Teva) diluted to 0.15mg/ml in Sodium Chloride 0.9% in a polyolefin infusion bag with and

without the Tevadaptor and indicates good stability in terms of loss of active, pH, appearance and sub-visible particle counts after 14 days in the refrigerator at 2-8°C protected from light.

New stability studies for fludarabine according to the European Pharmacopoeia 7.0, EJOP; 6, 1: 1-2. 2012, Trittler R.[4]

The study investigates the stability of the original vials with 25 mg/mL Fludarabine Phosphate (Teva) and infusion bags at concentrations of 0.04 mg/mL, 0.2 mg/mL and 1 mg/mL. A novel HPLC method was used which was shown to separate all related substances mentioned in the European Pharmacopoeia (and hence BP see above) during the method validation. During the stability trial, over 21 days in the refrigerator (2 – 8°C) and at room temperature, there was little change in the concentration of the active drug and no impurities were detected, the pH varied between dilutions but did not change significantly and there was no change in physical appearance. The conclusion based on a 5% loss of active was that Fludarabine Phosphate at 0.04 – 1.0mg/ml was stable for at least 21 days when stored at 8°C or at 25°C.

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. Data on File Physical and Chemical Stability of Fludarabine (Teva) (PL 00289/0938) Infusions, DOF 024a, (16/01/2013)
3. Studies on the stability and compatibility of cytotoxic drug infusion with the Tevadaptor system, EJOP; 8, 3: 26-30. 2014, Sewell G, Massimini M
4. New stability studies for fludarabine according to the European Pharmacopoeia 7.0, EJOP; 6, 1: 1-2. 2012, Trittler R.
SmPCs accessed on line or sent as part of the tender in June 2019