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: Vincristine Injection

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

7 days diluted to 0.02-0.1mg/ml in sodium chloride 0.9% in an infusion bag (product is also sometimes given in a syringe for paediatrics)

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

BP 2021 monograph for Vincristine Injection: Vincristine Injection is a sterile solution of Vincristine Sulfate in a suitable vehicle.

Content of Vincristine - 90.0 to 107.5% of the stated amount of anhydrous vincristine sulfate.

Related substances

Any secondary peak <2% (not greater than the area of the principal peak of a 1:50 dilution)

Sum of all secondary peaks <5% (not greater than 2.5x of the area of the principal peak of a 1:50 dilution)

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
Pfizer (Hospira UK Ltd) PL 04515/0043	The SmPC has no information on dilution or in-use shelf life	Solution for injection Mannitol Benzyl alcohol (9 mg per ml) Water for injections	Study provided from 1988 only 24-hour study and only 1 post T=0 datapoint[2]. Second study in syringes 28 days study at 5-8°C no degradation product analysis, sub-visible particles or data analysis, Report doesn't include T=0 results[3].	The studies supplied alone are not really useful but overall there is enough data to support 7 days shelf life for the product stored in a refrigerator diluted in sodium chloride 0.9% in bags or syringes.	See below
Teva UK Limited	Chemical and physical in-use stability of the solution prepared for injection or infusion has been demonstrated for 48 hours at 2-8°C or 24 hours at 15 - 25°C when diluted to a concentration range of 0.01 mg/ml to 0.1 mg/ml in 0.9% sodium chloride solution for infusion or in 5% glucose solution for infusion	Solution for injection Mannitol Sulfuric acid (for pH adjustment) Sodium hydroxide (for pH adjustment) Water for injections.	Study 0.01 - 0.1mg/ml in polyolefin bag and syringes. 84 days study data is inconsistent. No degradation product analysis, no replicates, no statistical analysis of data (which is variable). Concludes possible evidence of adsorption at low concentrations therefore to keep above 0.05mg/ml. concludes not to refrigerate but this does not seem to be a valid conclusion[4].	Product within the concentration limits 0.025 – 0.1mg/ml can be safely assigned a shelf life of seven days stored in a refrigerator in either polyolefin bags or polypropylene syringes.	Extended shelf life may be applied but see below for further guidance.

Conclusions (based on the data provided)

The first Hospira paper[2] only covers a 24 hour period and does indicate some loss of active over this period at room temperature although it is now a very old study and the data is not very useful. The Applied Analysis study[3] covers 28 days refrigerated storage but it was carried out on the neat solution (1mg/ml) and also diluted to 0.1mg/ml and 0.2mg/ml in syringes. These are not concentrations which are used in clinical practice today where 50ml minibags tend to be used for vincristine infusions with a concentration of 0.02 to 0.1mg/ml. The study was based on HPLC assay of active only, no degradation product analysis, no pH measurement and no sub-visible particle counts.

The Teva study[4] covers a period of 84 days and does have robust acceptance criteria (95 – 105% of initial concentration, pH within 1 unit, no change in appearance), although the data is very inconsistent for example the pH varies dramatically between time points (for example from 6.2 to 6.8 and then to 5.6 in a polyolefin bag), the pH is also significantly lower in syringes than in bags. Assay results for 0.01mg/ml are very inconsistent and show more than 5% loss at the first time point, this could be due to adsorption but levels have returned to nearly 99% of starting concentration by day 84. Data for concentrations of 0.025 to 0.1mg/ml show more consistent results at both 2 – 8°C and 25°C. The paper does indicate good stability of the molecule despite the data itself being inconsistent. There is no study of degradation product profile and without this, very long shelf lives are not supported by this paper alone.

Published studies

Stability of vincristine (TEVA) in original vials after re-use in dilute infusions in polyolefin bags and in polypropylene syringes: EJOP; 5,1: 10-14. 2011, Trittler R, Sewell G.[5]

This published paper covers the same data set as was submitted with this tender[4].

The stability of diluted vincristine sulfate used as a deterrent to inadvertent intrathecal injection: Hosp Pharm; 36: 740-745. 2001, Trissel LA, Zhang Y, Cohen MR.[6]

Physical stability was assessed using visual observation, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) assay. The paper covers 0.01 – 0.12mg/ml in bags (four doses each diluted in 25ml and 50ml) and 0.025 – 0.15mg/ml in syringes in sodium chloride 0.9% stored in a refrigerator for seven days (followed by 2 days at 23°C). The Eli Lilly branded product was used, this is a similar but not identical formulation to the above similarly containing mannitol but with parabens and an acetate buffer to control pH. Particle counts are only reported as no significant change, the HPLC assay showed no apparent loss of active throughout the

study (7 days refrigerated + 2 days at room temperature), there was no discussion on degradation product appearance or levels although the assay was validated as stability indicating. Overall despite falling short of today's expectations it is a good study and report within its limitations and does indicate no stability concerns within the concentration range studied.

Stabilité physico-chimique de la vincristine sans conservateur diluée en poche de NaCl 0,9 %; T. Henriet, N. El Kateb, N. Jourdan, P. Faure, P. Bellenger.Laboratoire de contrôle UPAC, Service de Pharmacie, Hôpital St-Louis, APHP, Paris (Poster)[7]

The poster covers concentrations of 0.033 – 0.121mg/ml in sodium chloride 0.9% stored at 4°C and 25°C and used the Teva product. The product remained stable (based on loss of active only) for seven days at both storage conditions. There was quite a variation in results but all solutions remained above 100% of the initial concentration throughout the study.

Stability of vinca alkaloid anticancer drugs in three commonly used infusion fluids: J Parenter Sci Technol; 43: 84-87. 1989, Beijnen JH, Vendrig DEMM, Underberg WJM.[8]

A fairly old paper which covered the stability of vincristine injection diluted to 0.02mg/ml in 0.9% sodium chloride, 5% dextrose, and Ringer's Lactate injection at 4°C and 25°C over three weeks based on HPLC assay of the active ingredient only.

Conclusion

There are no studies which cover the degradation products despite there being a BP monograph which includes a related substances test. There is also a degree of variation in assay results in many of the papers submitted or found. Despite this there is overall a clear picture that Vincristine diluted in sodium chloride 0.9% between 0.02 and 0.1mg/ml will be physically and chemically stable when stored at 2 – 8°C for seven days. This holds for both of the products listed in the table above. Beyond seven days there is some supportive data although it would be wise to understand the degradation product profile and whether this can be maintained within BP limits and also end of shelf life sub-visible particle counts.

Assessment carried out and report written by

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