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: **Docetaxel**

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

7 days at 0.3-0.74mg/ml at 2 – 8°C in Sodium Chloride 0.9% in infusion bag

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

Monograph for active ingredient only Docetaxel and Docetaxel Trihydrate

Related substances

- Impurity A <0.2% (<0.5% in the trihydrate)
- Impurity B <0.3%
- Impurity C <0.15%
- Impurity E <0.15%
- Unspecified Impurities <0.1%
- Total impurities <0.8% (<1.0% in the trihydrate)

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 EU/1/12/769/001 EU/1/12/769/002 EU/1/12/769/003	Physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2°C to 8°C.	Concentrate for solution for infusion. Polysorbate 80 Ethanol anhydrous Citric acid anhydrous	Study covering 0.3 - 0.9mg/ml in saline and dextrose over 98 days. Not compliant with YCD, no replicates, no degradation product analysis, no sub-visible particles which is important for Docetaxel.[2]	Although the study was lacking it does support 7 days shelf life stored in a refrigerator at 2 – 8°C. Label to check for particles before use and not use if particles are present.	See below
Fresenius Kabi EU/1/12/770/001 EU/1/12/770/002 EU/1/12/770/003 EU/1/12/770/004 EU/1/12/770/005	Physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2 to 8°C.	Concentrate for solution for infusion Polysorbate 80 Ethanol anhydrous Citric acid	N/A	No further data supplied support for 48 hours shelf life stored in a refrigerator at 2 – 8°C. Label to check for particles before use and not use if particles are present.	See below
Seacross PL 41013/0008	Physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2 to 8°C.	Concentrate for solution for infusion Polysorbate 80 Ethanol anhydrous Citric acid	No study submitted for this tender however, see below for further comment.	See below, study is available to support 7 days shelf life stored in a refrigerator at 2 – 8°C. Label to check for particles before use and not use if particles are present.	See below

Manufacturer	SmPC shelf life	Excipients / formulation details	Assessment of Extended studies submitted	Shelf-life recommendation (section 10 units)	Comments on further shelf life extension
Teva PL 30306/0261 (Docetaxel Actavis)	Physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated for 3 days when stored between 2 to 8°C protected from light. Docetaxel infusion solution is supersaturated, therefore may crystallize over time. If crystals appear, the solution must no longer be used and shall be discarded.	Concentrate for Solution for Infusion Citric acid anhydrous Povidone Polysorbate 80 Ethanol absolute	N/A	No further data supplied support for 72 hours shelf life stored in a refrigerator at 2 – 8°C. Label to check for particles before use and not use if particles are present.	See below

Conclusions (based on the data supplied)

It is important to acknowledge that precipitation is a risk with all Docetaxel preparations which are heavily solubilised. The precipitations seen do not seem to be concentration storage temperature or diluent specific and do seem to happen randomly.

Although Accord, Fresenius Kabi and Seacross have identical excipients, and Teva have the same plus Povidone, it must be stressed that variations in quantities will significantly impact on physical stability. The original Seacross formulation was an issue with additional precipitation incidents reported when it was launched, this led to its reformulation and changes in the level of Polysorbate 80[3]. Following this a new stability study was commissioned and indicated that the precipitation issue had been solved. This paper[4] outlines a study which is, more or less, NHS standards[1] compliant. It includes degradation products / related substances to both the BP / Ph Eur monograph and the USP monograph up to day 30 of the study and also looks at assay of the active alongside physical appearance and sub-visible particle counts for up to 90 days. Concentrations of 0.3 and 0.74mg/ml in both Dextrose 5% and Sodium Chloride 0.9% were included and showed good stability at 2 – 8°C throughout the study periods (adequate stability was also seen at room temperature 23 – 25°C). Hence it would be safe to apply at least a 30 days shelf life to the Seacross product made in a licensed unit within this concentration range and

possibly up to 90 days refrigerated. The product should still be labelled to check for particles before use and not to use if there are particles present, although no particles or significant increases in sub-visible particles, was seen throughout the study.

The Accord study, although covering 98 days was nowhere near to compliant with NHS standards[1] and is reliant on assay of the active ingredient and pH only, hence should not be used alone to support extended shelf life for the Accord preparation. The Teva and Fresenius Kabi products should be used in accordance with their SmPCs.

Published and other studies

Note that there have been changes to some manufacturers' products over the years, particularly with various mergers and demergers and also with the move away from products requiring two stage dilution which was the case with the original Taxotere product, this was changed to the 20mg/ml one stage dilution solution around 2010[7].

Physical and chemical stability of docetaxel infusions, EJHP; 17, 2: 39-43. 2011, MacLeod S, Sewell G.[5]

The study covers physical and chemical stability of 0.3 mg/mL and 0.7 mg/mL infusions of docetaxel (Teva) in polyolefin bags containing either 0.9% sodium chloride or 5% glucose, stored under refrigerated (2°C-8°C) and room temperature (25°C) conditions protected from the light. Chemical stability was determined using a validated stability-indicating, high performance liquid chromatography (HPLC) assay, degradation products were not assessed. Physical stability was determined using visual appearance, pH and sub-visual particulate counts. Results for both concentrations and diluents were satisfactory after 56 days storage at both refrigerated and room temperatures.

Stability of Docetaxel Solution after Dilution in Ethanol and Storage in Vials and after Dilution in Normal Saline and Storage in Bags, Can J Hosp Pharm ; 60, 4: 231-237. 2007, Walker S.E, Charbonneau F, Law S.[6]

Refers to a product requiring dilution with Ethanol diluent to 10mg/ml ahead of use and loos at the stability of the intermediate vial and the diluted final product. The diluted product studied was at 0.4 and 0.8mg/ml in Sodium Chloride 0.9% for 35 days and maintained more than 95% of starting concentration with no detected increase in degradation products. Visual inspection and pH assessments were carried out but no sub-visible particle counting is reported.

Taxotere 1-vial (docetaxel 20 mg/ml) physical and chemical stability over 28 days in infusion bags containing 0.9% saline solution and 5% glucose solution, EJOP ; 5,1: 24-27. 2011, Hart MC, Ahmed W[7]

The study was carried out following the launch of the one vial formulation of Docetaxel 20mg/ml and covered 0.8mg/ml solution diluted in Sodium chloride 0.9% in polyolefin bags. The solutions remained stable chemically and physically for the seven days storage period in the refrigerator followed by 24 hours at room temperature, study included appearance, assay for the active ingredient, degradation products and pH but not sub-visible particle counts. The study report does lack detail and was to support the launch of the new formulation.

Assessment carried out and report written by

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References

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