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: **Paclitaxel Injection**

This statement does **not** cover or apply to Paclitaxel Albumin (Abraxane)

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

7 days at 0.3 – 1.2mg/ml in Sodium Chloride 0.9% stored at room temperature.

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

No monograph for the injection, BP monograph exists for the starting material API including related substances tests for a large range or related substances Impurities A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q and R

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<br><br>PL 20075/0128 | Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 5°C and at 25°C for 7 days when diluted in 5% Dextrose solution, and for 14 days when diluted in 0.9% Sodium Chloride Injection. | Concentrate for Solution for Infusion.<br>Anhydrous ethanol<br>Polyoxyl 35 castor oil (Macrogolglycerol ricinoleate 35) | Study 0.1 - 1.2mg/ml fungal growth in most samples, data up to 14 days is Ok, no replicates, sub-visible particles (important for paclitaxel) or degradation products analysis[2]. | SmPC shelf life at 2-8°C and at 25°C for 7 days when diluted in 5% Dextrose solution or 0.9% Sodium Chloride Injection. Refrigerated storage is suggested. | SmPC shelf life at 2 - 8°C and at 25°C for 7 days when diluted in 5% Dextrose solution, and for 14 days when diluted in 0.9% Sodium Chloride Injection. Additional study does not add to this. |
| Fresenius Kabi<br><br>PL 08828/0186 | Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 25°C for 24 hours when diluted in 5% Glucose solution, 0.9% Sodium Chloride solution, 5% Glucose solution in Ringer solution, and 5% Glucose solution/0.9% Sodium Chloride solution. | Concentrate for solution for infusion.<br>Ethanol, anhydrous<br>Macrogolglycerol ricinoleate<br>Citric acid, anhydrous | Additional study supplied on request covering 0.3 - 1.2mg/ml in saline and dextrose. This was studied at 2 – 8°C and at room temperature with light protection. Some samples fail on particle counts even on day 0, others on other days of the study - this has been accepted by the manufacturer as a filter is needed during infusion. Lack of data points in some arms of study partially due to precipitations by day 21 (sometimes only two valid points). No statistical analysis of data although full related substances testing included and no problems seen.[3] | Additional study does support shelf life at 2 - 8°C and at 25°C protected from light for 7 days when diluted in 5% Dextrose solution or 0.9% Sodium Chloride Injection. Refrigerated storage is suggested. | Additional study does support shelf life at 2 - 8°C and at 25°C protected from light for 14 days when diluted in 5% Dextrose solution or 0.9% Sodium Chloride Injection. |

| 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)<br><br>PL 04515/0159 | Shelf life suggested within a table, between 0.3 and 1.2mg/ml at 2-8°C in the absence of light in non-PVC (polyolefin) infusion bags 28 days in Sodium Chloride 0.9% and 14 days in Dextrose 5%. At room temperature shelf life in both diluents is 72 hours. | Concentrate for solution for infusion.<br>Macrogolglycerol ricinoleate (polyoxyl castor oil)<br>Ethanol, anhydrous<br>Citric acid, anhydrous | N/A | SmPC shelf life at 2 - 8°C can be assigned as 7 days when diluted in 5% Dextrose solution or 0.9% Sodium Chloride Injection. | SmPC shelf life at 2 - 8°C can be assigned as 14 days when diluted in 5% Dextrose solution or 28 days when diluted in 0.9% Sodium Chloride Injection. |
| Seacross<br><br>PL 41013/0016 | Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 2°C to 8°C and at 25°C for 7 days when diluted in 5% dextrose solution, 5% dextrose and 0.9% sodium chloride solution and for 14 days when diluted in 0.9% sodium chloride injection. | Concentrate for Solution for Infusion<br>Citric acid anhydrous<br>Ethanol anhydrous<br>Polyoxyl castor oil (Cremophor) | N/A | SmPC shelf life at 2-8°C and at 25°C for 7 days when diluted in 5% Dextrose solution or 0.9% Sodium Chloride Injection. Refrigerated storage is suggested. | SmPC shelf life at 2 - 8°C and at 25°C for 7 days when diluted in 5% Dextrose solution, and for 14 days when diluted in 0.9% Sodium Chloride Injection. |

| 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 UK Limited<br><br>PL 00289/0859 | Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 5°C and at 25°C for 14 days when diluted in 50 mg/ml (5%) glucose solution for infusion or in 9 mg/ml (0.9%) sodium chloride solution for infusion. | Concentrate for solution for infusion. Ethanol, anhydrous Citric acid, anhydrous Macrogolglycerol ricinoleate | Two studies at 0.3 - 1.2mg/ml at 2-8°C and 25°C fails at day 15, sub-visible particles increase over the study. Presentation of results poor. No degradation product analysis, no statistical analysis of data.[4,5]<br>These studies do not really support the SmPC shelf life. | SmPC shelf life at 2-8°C and at 25°C for 7 days when diluted in 5% Dextrose solution or 0.9% Sodium Chloride Injection. Refrigerated storage is suggested | SmPC shelf life at 2-8°C and at 25°C for 14 days when diluted in 5% Dextrose solution or 0.9% Sodium Chloride Injection. Additional study does not add to this. |

Conclusions (based on the data provided)

Within the Fresenius Kabi paper[3] there is assessment of a range of degradation products all of which are below the limit of quantification throughout the studies, the degradation of Paclitaxel is by hydrolysis to 10-O-Deacetylpaclitaxel (Impurity G) and Baccatin III (Impurity N) and also epimerisation to 7-Epipaclitaxel (impurity E), none of which were detected during the study. There was some evidence of a small loss of active drug over time (but no statistical analysis) although the shelf life limiting criterion is the precipitation of the product which was shown to occur after day 21. Sub-visible particle counts were high throughout the studies including on day 0, FK accept this as the product is filtered during administration, but it is likely that these particles are acting as a focus to eventually bring about precipitation.

The studies supplied by Teva[4,5] do not really support the full shelf life in the SmPC although it is assumed that they do have data to support this in the regulatory submission. The papers do stress that the issue with Paclitaxel is physical stability rather than chemical degradation and the papers do stress that stability is better on refrigerated storage than storage at room temperature.

Hence there is sufficient data to support a seven day shelf life for all products stored at 2 – 8°C in Dextrose 5% and Sodium Chloride 0.9%, refrigerated storage is recommended despite the CMU requirement for room temperature data. There is some data to support shelf lives longer than this for products

made within licensed units but, in most cases, this is limited to 14 days. All products listed have a similar formulation, although some list Citric acid for pH adjustment, bearing in mind the instability of the product is largely a physical instability extrapolation of data between products is not recommended. Infusions of Paclitaxel should be labelled to check before administration and to not use if particles / precipitation is present.

Published and other relevant reports

Long-term physical and chemical stability of a generic paclitaxel infusion under simulated storage and clinical-use conditions: EJHP Science; 12, 6: 129-134. 2006, Kattige A.[6]

The study looked at 0.3, 0.75 and 1.2mg/ml concentrations in Sodium Chloride 0.9% and Dextrose 5% and looked at chemical and physical stability but not degradation products. Shelf life at 2 – 8°C was suggested as between 12 and 28 days dependant on concentration, at room temperature the shelf life was between 4 and 8 days dependant on concentration and diluent.

Physical and Chemical Stability of Paclitaxel Infusions in Different Container Types, J Oncol Pharm Pract. 2006 Dec;12(4):211-22, P. Donyai, G. Sewell[7]

The paper covered the stability of generic (Teva Pharmaceuticals) Paclitaxel infusions (0.3 and 1.2 mg/mL) in 0.9% Sodium Chloride or 5% Dextrose in polyolefin (Viaflo), low-density polyethylene (Ecoflac), and glass containers at 2-8 and 25°C. Precipitation was the limiting factor with shelf life suggested as between 8 and 20 days when stored at 2 – 8°C depending on concentration and diluent and 3 to 7 days at room temperature. It is likely that this paper is based on the study reports submitted by Teva for assessment for this tender.

These studies do not add anything to the above assessment but reinforce the conclusions.

DEHP leaching

The SmPCs for Paclitaxel preparations contain the following (or similar) statement: Polyoxyethylated 35 castor oil can result in DEHP (di-(2-ethylhexyl)phthalate) leaching from plasticised polyvinyl chloride (PVC) containers, at levels which increase with time and concentration. Consequently, the preparation, storage and administration of diluted paclitaxel should be carried out using non-PVC-containing equipment, in some cases this is stated as non-PVC-containing equipment such as glass, polypropylene, or polyolefin. The administration instructions also include reference to using polyethylene-lined administration sets.

Non-DEHP (non-phthalate) PVC administration sets are now freely available and in common use and are suitable for use with Paclitaxel infusions as there is no DEHP / phthalate to leach from within these.

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. Physical and Chemical in-use stability of Paclitaxel 6mg/ml Concentrate for solution for infusion (Accord Healthcare) 04/02/14
3. Stability statement of Paclitaxel Kabi (Concentrate for solution for infusion) 6mg/ml diluted on 0.9% sodium chloride and 65% glucose in Freeflex containers SU550/09
4. Stability studies of Paclitaxel (Teva) infusions 10th August 2009 DOF002b
5. Stability studies of Paclitaxel (Teva) infusions in Ecoflac containers 10th August 2009 DOF002c
   SmPCs accessed on line July 2020 or supplied as part of the tender in June / July 2019.
6. Kattige A. Long-term physical and chemical stability of a generic paclitaxel infusion under simulated storage and clinical-use conditions. Eur J Hosp Pharm Sci 2006;12(6):129 -134.
7. Donyai P, Sewell GJ. Physical and chemical stability of paclitaxel infusions in different container types. J Oncol Pharm Pract. 2006;12(4):211-222. doi:10.1177/1078155206073589