

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 products¹.

Drug: Carboplatin

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

7 days at 2 – 8°C at 0.2 – 3.5 mg/ml in Dextrose 5% in an infusion bag

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

BP 2020 monograph Carboplatin Injection

Content of carboplatin 90.0 to 105.0% of the stated amount.

The impurities limited by the requirements of this monograph include those listed in the monograph for Carboplatin raw material. There is a specific increased limit listed for Impurity B (cyclobutane-1,1-dicarboxylic acid) of 1.0% the other limits are as in the raw material monograph of 0.25% for Impurity A (Cisplatin) with 0.1% for individual unspecified impurities and 0.5% for total unspecified impurities.

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 20075/0028	Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature and 30 hours at 2-8°C.	10 mg/ml concentrate for solution for infusion Water for Injections	2017 report 0.3 - 3mg/ml No sub-visible particles, no statistical analysis of data, time T= 63days very out of trend and out of spec. not discussed. No increase in degradation products seen in 63 day study. ²	Study deemed sufficient to support 7 days in glucose 5% (in sodium chloride 0.9% 24 hours borderline).	Study is well short of NHS standards ¹
Consilient (Hikma) PL 15413/0068	Carboplatin may be diluted in Dextrose 5% or Sodium Chloride 0.9% and administered as an intravenous infusion. These solutions for infusion are chemically stable for up to 24 hours when stored at 2-8°C and up to 8 hours when stored at 22°C.	10 mg/ml concentrate for solution for infusion Water for injections Hydrochloric acid (pH adjustment) Sodium hydroxide (pH adjustment)	Hikma (Thymoorgan Pharmazie) 0.3 - 7mg/ml 2-8°C and 15-25°C 72 hours. Full range of tests but only three data points post T=0..Dextrose 5% results OK for 72 hours but lack data points and replicates. Sodium chloride 0.9% 0.3mg/ml out of specification (OOS) at 24 hours at room temperature and degradation products OOS in fridge and ambient ³	Study deemed sufficient to support 3 days in glucose 5%. SmPC supports 24 hours in sodium chloride 0.9%.	No data provided
Fresenius Kabi PL 18727/0025	Chemical and physical in-use stability has been demonstrated after dilution in Glucose 5 % for 96 hours at 2°C to 8°C and 20°C to 25°C. Chemical and physical in-use stability has been demonstrated after dilution in Sodium Chloride 0.9% for 24 hours at 2°C to 8°C and 8 hours 20°C to 25°C.	10 mg/ml concentrate for solution for infusion Water for Injections	Further study submitted retrospectively covering 0.2 - 5.0mg/ml in Glucose 5% at refrigerated and room temperature for 84 days. Study is mainly compliant with the standards ¹ and includes degradation product analysis and sub-visible particulates. Both concentrations stable in a refrigerator throughout 84 days study. 0.2mg is less stable at room temperature and hence refrigerated storage is recommended. ⁴	Study deemed sufficient to support 7 days in glucose 5%. SmPC supports 4 days in glucose 5%. SmPC supports 24 hours in sodium chloride 0.9%.	Good quality study provided to support extended shelf life in Glucose 5% (see comments 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
Pfizer (Hospira UK Ltd) PL 04515/0050	Carboplatin solution for infusion may be further diluted in Glucose 5% and administered as an intravenous infusion. Chemical and physical in-use stability has been demonstrated for 56 days to final concentrations of 0.2 mg/ml and 3.5mg/ml when stored at 2-8 °C in non-PVC (polyolefin) infusion bags when protected from light. Carboplatin solution for infusion may also be further diluted in Sodium Chloride 0.9% and administered as an intravenous infusion. The infusion solution is chemically stable for up to 24 hours when stored at 2-8°C and up to 8 hours when stored at 22°C	10 mg/ml intravenous infusion Water for Injections	N/A	SmPC sufficient to support 7 days in glucose 5%. SmPC supports 24 hours in sodium chloride 0.9%.	SmPC sufficient to support 56 days in glucose 5%.
Teva UK Limited PL 00289/0847	When reconstitution/dilution is carried out under validated aseptic conditions, and if justified, the product may be stored for a maximum period of 24 hours (at 2–8°C).'	10 mg/ml concentrate for solution for infusion. Mannitol Water for Injections	Study in saline for 7 days at 2-8°C and in dextrose 91 days at 2-8°C and ambient. No degradation product analysis, very poor quality report. Second study includes pH and sub-visible particles 0.7 - 2.15mg/ml in glucose. No replicates or degradation product analysis but 84 day study.	Study deemed sufficient to support 7 days in glucose 5%. SmPC supports 24 hours in glucose 5% or sodium chloride 0.9%. (see below for comment)	The studies supplied are indicative of extended stability although are of poor quality.

Conclusions (based on the data supplied)

When diluted in Dextrose every indication including the Pfizer (Hospira) SmPC indicate that the drug is relatively stable and can safely be assigned a seven day shelf life in section 10 aseptic units and longer in licensed units across a wide concentration range. The Accord, Fresenius Kabi and Pfizer preparations are simple solutions in Water for Injections, and the Consilient (Hikma) product only differs in mentioning pH adjustment in the SmPC. The Teva product has a different formulation which contains Mannitol.

The Fresenius Kabi paper⁴ does allow the Impurity B limits to exceed that of the BP significantly justifying the position by stating that both impurities are metabolites of carboplatin. However, the results do indicate that within the refrigerated storage the BP limit (0.5%) is not exceeded for either concentration throughout the 84 day study, at room temperature the 0.2mg/ml solution does significantly exceed the BP limit from day 14 (the first post T=0 data point). Hence it is suggested that all infusions should be stored in the refrigerator.

The drug may also be diluted in 0.9% sodium chloride, however, nucleophilic attack by chloride ions can convert part of the carboplatin to chloride-substituted derivatives, including cisplatin. The mono- and di-chloride platinum species can then react with water to produce toxic aquated platinum adducts⁷⁻⁹. The inconsistency of data above and published studies would indicate that a shelf life in sodium chloride 0.9% should probably not exceed 24 hours despite the data reported by Teva and the study referenced below.

Published studies

A sequential temperature cycling study for the investigation of carboplatin infusion stability to facilitate 'dose-banding'. J Oncol Pharm Practice ; 13: 119-126. 2007, Kaestner S, Sewell G.¹⁰

Carboplatin infusions at 0.70 and 2.15 mg/mL, were stored refrigerated for up to 84 days, followed by incubation at 25°C for 24 h. The infusions were also returned to refrigerated storage for 3 and 7 days to simulate return unused. Chemical and physical stability were determined by HPLC, sub-visual particulate counts, pH-measurement. Both concentrations were chemically and physically stable following refrigerated storage, with light protection, for 84 days, followed by a further 24 hours at 25°C and following return to refrigerated storage for at least 7 days.

Studies on the stability and compatibility of cytotoxic drug infusion with the Tevadaptor system, EJOP; 8, 3: 26-30. 2014, Sewell G, Massimini M.¹¹

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 Carboplatin (Teva) at 2mg/ml in Dextrose 5% in polyolefin bags, 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°C protected from light.

Stability study of carboplatin infusion solutions in 0.9% sodium chloride in polyvinyl chloride bags. J Oncol Pharm Practice ; 22: 31-36. 2016, Myer A.Ls, Zhang Y-P, Kawedia L, Trinh V.A, Tran H, Smith J.A, Kramer M.A.¹²

The physico-chemical stability of 0.5 mg/mL, 2.0 mg/mL, and 4.0 mg/mL carboplatin diluted in sodium chloride 0.9% in PVC bags was determined following storage at room temperature under ambient fluorescent light and under refrigeration in the dark for seven days. Assay was by HPLC for active only and storage at 4°C, all tested solutions were found to be chemically stable for at least seven days, with nominal losses of ≤6%. At room temperature exposed to normal fluorescent light, the chemical stability of 0.5 mg/mL, 2.0 mg/mL, and 4.0 mg/mL solutions was determined to be three days, five days, and seven days, respectively

Assessment carried out and report written by

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