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: **Irinotecan**

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

7 days stored in a refrigerator at 2 – 8°C at up to 3mg/ml in Sodium Chloride 0.9%

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

No Monograph for Irinotecan Injection, monograph in the 2020 BP for Irinotecan Hydrochloride Trihydrate API

Monograph includes tests for enantiomeric purity and related substances tests for impurities C (8-ethyl irinotecan), E (11-ethyl-9-hydroxycamptothecin) and M (12-hydroxy irinotecan) and unspecified impurities as well as the total 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 20075/0443	Irinotecan solution is physically and chemically stable with infusion solutions (0.9% (w/v) sodium chloride solution and 5% (w/v) glucose solution) for up to 28 days when stored in LDPE or PVC containers at 5°C or at 25°C and protected from light. When exposed to light, physico-chemical stability has been demonstrated for up to 3 days.	Concentrate for solution for infusion Sorbitol Lactic acid Sodium hydroxide (for pH-adjustment) Hydrochloric acid (for pH-adjustment) Water for injections	Study 0.12 - 2.5mg/ml in Polyolefin bag and 20mg/ml in syringe. No replicates, no degradation product analysis no sub-visible particle analysis. Study 84 days at 20 – 25°C protected from light. Note light exposure has a significant impact on stability.[2]	SmPC shelf life seven days (recommended refrigeration at 2 – 8°C) in Sodium Chloride 0.9% or Glucose 5% protected from light.	SmPC shelf life 28 days (recommended refrigeration at 2 – 8°C) in Sodium Chloride 0.9% or Glucose 5% protected from light. Probably stable for longer (see below).
Consilient (Hikma) PL 15413/0065	After dilution with 5% glucose, physical and chemical stability was demonstrated for 24 hours, when stored between 2-8°C and for 12 hours if stored between 15-30°C. After dilution with 0.9% sodium chloride, physical and chemical stability was demonstrated for 12 hours if stored between 15-30°C.	Concentrate for solution for infusion Sorbitol Lactic acid Sodium hydroxide and/or Hydrochloric acid (for pH adjustment to 3.5) Water for injection	Updated following 2020 tender submission: Study submitted refers to Ebewe product with statement that this is identical to the Hikma product[10]. The study itself[11] provides data for up to 28 days at 2 – 8°C and 20 – 25°C protected from light between 0.12 and 2.8mg/ml. Light exposure did cause some instability.	A shelf life of seven days stored in a refrigerator (2 – 8°C) can safely be applied to the product in Sodium Chloride 0.9% or Glucose 5% protected from light.	Study supports a shelf life of 28 days (recommended refrigeration at 2 – 8°C) in Sodium Chloride 0.9% or Glucose 5% protected from light.

Manufacturer	SmPC shelf life	Excipients / formulation details	Assessment of Extended studies submitted	Shelf-life recommendation (section 10 units)	Comments on further shelf life extension
Fresenius Kabi PL 18727/0007	After dilution: Chemical and physical in-use stability has been demonstrated for 24 hours below 25°C and for 48 hours at 2°C to 8°C.	Concentrate for Solution for Infusion. Sorbitol, Lactic acid, Water for Injections, Sodium hydroxide (for pH adjustment).	Retrospectively a study report was supplied covering 0.4 - 2.8mg/ml dilutions in Glucose 5% and Sodium Chloride 0.9% over an 84-day period. Study is mainly compliant with the standards document[1] including full degradation product analysis and sub-visible particle counts. The data would have benefited from statistical regression analysis. However, the data set is good enough to safely assign a seven-day shelf life.[3]	A shelf life of seven days stored in a refrigerator (2 – 8°C) can safely be applied to the product in Sodium Chloride 0.9% or Glucose 5% protected from light.	Data does support extended stability possibly up to 84 days stored in a refrigerator (2 – 8°C) in Sodium Chloride 0.9% or Glucose 5% protected from light.
Medac PL 11587/0047	After dilution in 0.9 % sodium chloride solution or 5 % glucose solution, chemical and physical in-use stability has been demonstrated for up to 6 hours at room temperature (approximately 25 °C) and ambient lighting or 48 hours if stored at refrigerated temperatures (approximately 2 °C – 8 °C).	Concentrate for solution for infusion Sorbitol Lactic acid Sodium hydroxide (to adjust to pH 3.5) Water for injections	Additional study supplied covering 0.4 – 3.0mg/ml over 84 days stored in a refrigerator (2 – 8°C) and 45 days at room temperature (15 °C – 25 °C) in Sodium Chloride 0.9% and Glucose 5% and at 20mg/ml in a syringe. Not all tests carried out after day 30 but little loss of active seen after 84 days in a refrigerator. No sub-visible particle analysis and lack of detail within report.[4]	A shelf life of seven days stored in a refrigerator (2 – 8°C) can safely be applied to the product in Sodium Chloride 0.9% or Glucose 5% protected from light.	Data does support extended stability at least up to 30 days stored in a refrigerator (2 – 8°C) protected from light.

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 Ltd) Hospira UK PL 04515/0227	Chemical and physical in-use stability has been demonstrated in glucose 50 mg/ml (5%) and in sodium chloride 9 mg/ml (0.9%) for 72 hours at 2-8 °C.	Concentrate for Solution for Infusion Sorbitol Lactic acid Sodium hydroxide and/or hydrochloric acid (for pH adjustment) Water for Injections	SmPC for Campto branded product (not supplied on the tender) does have extended data for up to 28 days within it. There is also a stability study for the Hospira Irinotecan found on PharmaQC (but not submitted) which is for 0.4mg - 2.8mg/ml in saline and Glucose for 84 days. The report lacks any information on degradation products.[6]	A shelf life of seven days stored in a refrigerator (2 – 8°C) can safely be applied to the product in Sodium Chloride 0.9% or Glucose 5% protected from light.	Data does support extended stability at least up to 30 days stored in a refrigerator (2 – 8°C) protected from light.
Seacross PL 41013/0001	Chemical and physical in-use stability of the drug product after dilution in the recommended solutions for infusion (0.9% sodium chloride solution or 5% glucose solution) has been demonstrated for 6 hours at 25°C±2°C and for 24 hours at 2°C -8°C	Concentrate for solution for infusion Sorbitol Lactic Acid Sodium Hydroxide (for pH adjustment) Water for injection Hydrochloric acid (for pH adjustment)	Additional study on Pharma QC. Irinotecan infusions at concentrations of 0.12 and 2.8 mg/ml in 0.9% Sodium Chloride and 5% Glucose stored in Polypropylene bottles under 25°C and 2-8°C storage condition. Data is good although no degradation products assessed and no statistical data analysis (does include sub-visible particles) study for 30 days.[7]	A shelf life of seven days stored in a refrigerator (2 – 8°C) can safely be applied to the product in Sodium Chloride 0.9% or Glucose 5% protected from light	Data does support extended stability possibly up to 30 days stored in a refrigerator (2 – 8°C) in Sodium Chloride 0.9% or Glucose 5% protected from light.

Conclusions (based on the data provided)

The Accord study shows some loss of active at the higher (2.5mg/ml) concentration during the study but this stays within 95 – 105% throughout the 84 days in both Sodium Chloride 0.9% and Glucose 5%. The 0.12mg/ml shows little change in the concentration of active throughout the study.

The Fresenius Kabi study would have benefitted from statistical analysis of the data as there are some inconsistencies in some of the active concentration data across the studies (particularly the lower concentration in saline in the refrigerator). Otherwise this is a good study and does include analysis of degradation products.

Pfizer provided some information relating to the submitted Hospira product but also some data for Campto (their original licensed product) PL 00057/0626 (hence different to the Hospira product). The product appears to be identical in constituents and to the Hospira product and also mentions pH adjustment to 3.5 in the SmPC. This states in the SmPC '*CAMPTO solution is physically and chemically stable with infusion solutions (0.9% (w/v) sodium chloride solution and 5% (w/v) glucose solution) for up to 28 days when stored in LDPE or PVC containers at 5°C or at 30°C and protected from light. When exposed to light, physico-chemical stability has been demonstrated for up to 3 days*'[5] The Hospira extended study[6] did report out of specification sub-visible particle counts at day 84 for the 2.8mg/ml diluted in Sodium Chloride 0.9%.

Consilient (Hikma) submitted a study carried out on the identical Ebewe product[11], this showed stability for 28 days protected from light at 2 – 8°C and 20 – 25°C in a variety of containers, based on loss of active, appearance of degradation products, pH and appearance. When exposed to light the levels of one degradation product (Camptothecin) increase significantly and hence light protection is required.

All of the products tendered have identical excipients and those that do state a pH for adjustment state to pH 3.5 (It is safe to assume that all products will have a similar pH for maximum stability. With a suitable margin of safety, it would be acceptable to extrapolate the data available to cover any of the brands listed and for section 10 units to assign a seven-day shelf life to the product in Sodium Chloride 0.9% or Glucose 5% stored in a refrigerator (2 – 8°C) and protected from light. For licenced units a longer shelf life can safely be assigned for at least 30 days and probably much longer under the same conditions. Light protection is of paramount importance as the product is unstable when exposed to light.

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.[8]

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 Iriniotecan (Teva) at 1mg/ml in Sodium Chloride 0.9% 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^{o}C protected from light.

Physicochemical stability of irinotecan injection concentrate and diluted infusion solutions in PVC bags, J Oncol Pharm Practice ; 6, 3: 115-121. 2000, Thiesen J, Krämer I.[9]

The study looked at Irinotecan infusion solutions after dilution in Sodium Chloride 0.9% and Glucose 5% in PVC bags, stored under refrigeration (2-8°C) or at room temperature either light protected or exposed to light (mixed daylight and normal laboratory fluorescent light), covering concentrations of 0.4, 1.0 and 2.8 mg/ml. Analysis included stability-indicating HPLC assay, pH and appearance. Solutions are shown to be physico-chemically stable (defined as >90% Irinotecan) for 4 weeks when stored under refrigeration or light protected at room temperature, independent of the vehicle (Sodium Chloride 0.9% and Glucose 5%) and of the concentration (0.4, 1.0, or 2.8 mg/ml). Irinotecan infusion solutions exposed to daylight exhibited concentration-dependent instability, solutions were stable for only 7 to 14 days.

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