

## Background

In order to provide NHS aseptic units with information on which to base the shelf-life of aseptically compounded products a series of stability assessments has been undertaken.

The studies provided have been reviewed against the standards of the NHS standards for stability testing of small molecule drug aseptic products<sup>1</sup>.

## Drug: Ganciclovir

### Requirements for shelf life

For a product such as ganciclovir it would be beneficial to have a shelf-life of at least seven days stored in a refrigerator across a range of clinically acceptable concentrations.

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

The BP has no monograph for Ganciclovir injection only for the Active Pharmaceutical Ingredient

### Related substances listed in the API monograph

Impurity F (guanine) not more than 0.4%

Impurity B not more than 0.2%

Impurities A, C, D, E each not more than 0.15%

Unspecified impurities not more than 0.05%

Total impurities not more than 0.6

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
Reig Jofre UK Limited PL 25174/0033	<p>After reconstitution: Chemical and physical in-use stability has been demonstrated for 12 hours at 25°C. After dissolving with water for injections. Do not refrigerate or freeze.</p> <p>After dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at 2° to 8° C.</p>	<p>Powder for concentrate for solution for infusion. No excipients</p>	N/A	<p>See below discussion. It should be safe to assign a seven-day shelf life for the ready to administer presentation 0.25 mg/mL - 5 mg/mL in 0.9% sodium chloride stored at 2 – 8°C. There is also sufficient data to support room temperature storage to allow for extended infusion times if required.</p>	<p>See Below for guidance if assigning a longer shelf life</p>
Cheplapharm Arzneimittel GmbH (Cymevene) PL 27041/0013	<p>After reconstitution: Chemical and physical in-use stability has been demonstrated for the reconstituted product for 12 hours at 25°C after dissolving with water for injections. Do not refrigerate or freeze.</p> <p>After dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at 2 – 8°C (do not freeze).</p>	<p>Powder for concentrate for solution for infusion.  Sodium hydroxide Hydrochloric acid (for pH-adjustment)</p>	N/A	<p>See below discussion. It should be safe to assign a seven-day shelf life for the ready to administer presentation 0.25 mg/mL - 5 mg/mL in 0.9% sodium chloride stored at 2 – 8°C. There is also sufficient data to support room temperature storage to allow for extended infusion times if required.</p>	<p>See Below for guidance if assigning a longer shelf life</p>

#### Published studies

Stability and compatibility of ganciclovir sodium in 5% dextrose injection over 35 days: Am J Hosp Pharm ; 48: 2641-2643. 1991, Silvestri AP, Mitrano FP, Baptista RJ, Williams DA.<sup>2</sup>

The stability and compatibility of ganciclovir sodium in 5% dextrose injection over 35 days were assessed. Nine admixtures of ganciclovir sodium 1, 5, and 10 mg/mL in 5% dextrose injection were aseptically prepared. The admixtures were stored in the dark at 4-8°C and sampled at 10 and 35 days. There was no significant loss of ganciclovir over the 35-day study period but a high degree of variation especially based on only two time points (range 93.4% to 103.7% of initial ganciclovir concentration). There were no appreciable pH changes, and there was no evidence of visual incompatibility. Ganciclovir sodium 1, 5, and 10 mg/mL in 5% dextrose injection was deemed to be stable for at least 35 days when stored in the dark at 4-8°C.

Stability of ganciclovir sodium (Cymevan\*) after dilution in PVC infusions and polypropylene syringes: J Pharm Belg ; 47: 494-498. 1992, Phaypradith S, Vigneron J, Perrin A, Durney-Archeray MJ, Hoffman MA, Hoffman M.<sup>3</sup>

The stability of ganciclovir sodium solutions was tested in 0.9% sodium chloride at three concentrations 70, 200 and 350 mg/50 ml for polypropylene syringes, and two concentrations (70 and 350 mg/250 ml) for PVC bags and at three temperatures (-20 degrees C, + 4 degrees C, room temperature). The solutions, which had been initially frozen, were thawed by microwave. The stability of each sample was determined by high-performance liquid chromatography. The results of this study indicate that admixtures of ganciclovir sodium at the concentration rates tested can be frozen for at least one year and are stable for at least 80 days at + 4 degrees C and 7 days at room temperature.

Long-term stability of ganciclovir in polypropylene containers at room temperature. Journal of Oncology Pharmacy Practice; Mar 2019; vol. 25 (no. 2); p. 303-308, Guichard N, Bonnabry P, Rudaz S, Fleury S.<sup>4</sup>

The objective of this study was to develop a stability-indicating method to assay ganciclovir and determine the stability of ganciclovir in syringes (5 mg/mL) and infusion bags (0.25 and 5 mg/mL) at two different temperatures. Ganciclovir solutions (Cymevane – Roche) (0.25 mg/mL and 5 mg/mL) in 0.9% sodium chloride were prepared in 50 mL polypropylene syringes or 100 mL polypropylene infusion bags and stored at 2–8°C and 23–27°C. The chemical stability was measured using a stability-indicating Ultra High Performance Liquid Chromatography coupled to a twin mass spectrometry method. Physical stability was assessed by visual inspection only, no sub-visible particle counts were carried out. No significant loss of ganciclovir under any of the tested conditions was observed in this study. All solutions remained clear through the study period. All tested formulations remained stable for at least 185 days independently of container type, temperature or concentration studied although there was some inconsistency in the data and the day 70 data for all samples was borderline if using 95 – 105% acceptance criteria. There is no reporting of the degradation product profile not a comment on the presence or absence of degradation products in the stability phase of the study.

## Conclusions

The two products are free of excipients with the exception of the potential for pH adjustment in the Cheplapharm (originator) product. Hence it would be safe to extrapolate data for the diluted products from one brand to the other. Ganciclovir was much studied in the 1990s but only two studies from that time have been deemed worthy of inclusion here. The modern paper<sup>4</sup> is robust from the loss of active angle but does not consider the degradation products profile nor were sub-visible particles measured just physical appearance. There is no BP monograph for the injection and hence no limits for related substances to apply (apart from those in the starting material which may not be relevant to the injection particularly in ready to administer presentations).

The papers do indicate that the drug is relatively stable and even without the degradation product profile and sub-visible particle count results it would be safe to use them to assign a seven-day shelf life for the ready to administer presentation 0.25 mg/mL - 5 mg/mL in 0.9% sodium chloride in polypropylene syringes or infusion bags and stored at 2–8°C. There is also sufficient data to support room temperature storage to allow for extended infusion times if required. Potentially a longer shelf life could be safely applied in licensed units although it would be good to understand the sub-visible particle counts at the end of this shelf life and the related substances profile.

The Silvestri paper<sup>2</sup> does have data for concentrations up to 10mg/ml and this still appears to be satisfactory for refrigerated storage, the reconstituted solution should, according to the SmPCs, not be stored refrigerated and hence 10mg/ml should be the maximum concentration produced and stored in a refrigerator.

Assessment carried out and report written by

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Chair of the NHS Pharmaceutical Research and Development Group. 5<sup>th</sup> November 2020

## 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. Stability and compatibility of ganciclovir sodium in 5% dextrose injection over 35 days: Am J Hosp Pharm ; 48: 2641-2643. 1991, Silvestri AP, Mitrano FP, Baptista RJ, Williams DA.#
3. Stability of ganciclovir sodium (Cymevan\*) after dilution in PVC infusions and polypropylene syringes: J Pharm Belg ; 47: 494-498. 1992, Phaypradith S, Vigneron J, Perrin A, Durney-Archeray MJ, Hoffman MA, Hoffman M.
4. Long-term stability of ganciclovir in polypropylene containers at room temperature. Journal of Oncology Pharmacy Practice; Mar 2019; vol. 25 (no. 2); p. 303-308, Guichard N, Bonnabry P, Rudaz S, Fleury S.