Background

As part of a review of stability data for cytotoxic drugs, 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: **Mitomycin Injection**

NHS requirements for shelf life / preparations prepared

The product is prepared for intravenous, intravesical and ophthalmic uses. A usable shelf life is required to allow aseptic services preparation of the range of products

British Pharmacopoeia specification for product.

The BP2020 has no monograph for Mitomycin injection nor for other prepared products. There is a monograph for the Mitomycin starting material (API) (Mitomycin C), this states that it is produced by a strain of Streptomyces caespitosus. The monograph includes related substances tests for Impurities A (cinnamamide), B (mitomycin A), C (mitomycin B) and D (albomitomycin C), the limits for each in the starting material are 0.5% (based on the active).

The USP does have a monograph for Mitomycin injection which has limits of 90 – 120% of stated amount of Mitomycin.

Assessment:

Manufacturer	SmPC shelf life	Excipients / formulation details	Other comments	Shelf-life recommendation
Accord PL 20075/0387 (2mg) PL 20075/0388 (10mg) PL 20075/0389 (20mg)	The reconstituted product should be used immediately.	Powder for solution for injection/infusion or intravesical use. Mannitol (confirmed as a 2:1 ratio Mannitol to Mitomycin)[2]	Intravenous use: Mitomycin 10 mg, powder for solution for injection/infusion or intravesical use may not be reconstituted in water. The contents of the vial should be reconstituted with saline or 20% glucose solution in a ration of 10 ml for the 10 mg of mitomycin. Intravesical use: Mitomycin 10 mg, powder for solution for injection/infusion or intravesical use may not be reconstituted in water. The contents of the vial should be reconstituted with saline or phosphate buffer 7.4 in a ration of 10 ml for the 10 mg of mitomycin.	See below
Accord PL 20075/0515	The reconstituted product should be used immediately.	Powder for solution for injection/infusion Mannitol (confirmed as a 2:1 ratio Mannitol to Mitomycin)[2]	Mitomycin 40 mg powder for solution for injection/infusion may not be reconstituted in water. The contents of the 40 mg vial should be reconstituted with 80 ml saline or 20% glucose solution. The contents of the 40 mg vial cannot be reconstituted to a concentration of 1 mg/mL. Other products should be used if this concentration is needed.	See below

Manufacturer	SmPC shelf life	Excipients / formulation details	Other comments	Shelf-life recommendation
Accord (for USA market) NDC 16729-115-05 (5 mg) NDC 16729-108-11 (20 mg) NDC 16729-116-38 (40 mg)	Reconstituted with Sterile Water for Injection to a concentration of 0.5 mg per mL, mitomycin is stable for 14 days refrigerated or 7 days at room temperature. Diluted in sodium chloride 0.9% at room temperature, to a concentration of 20 to 40 micrograms per mL: 12 hours.	Each vial contains either mitomycin 5 mg and mannitol 10 mg, mitomycin, 20 mg and mannitol 40 mg or mitomycin 40 mg and mannitol 80 mg.	To administer, add Sterile Water for Injection, 10 mL, 40 mL or 80 mL respectively.	Reconstituted with Sterile Water for Injection to a concentration of 0.5 mg per mL, mitomycin is stable for 14 days refrigerated Reconstituted in Water for Injection and diluted in Sodium Chloride 0.9% to between 20 to 40 micrograms per mL: 12 hours stored in a refrigerator (2 – 8°C)
Accord (for Australian market) Omegapharm Pty Ltd	Reconstituted with water for injection (mitomycin concentration 0.5 mg/mL to 1 mg/mL), it is stable for 24 hours when protected from light and stored in a cool place. (refrigerate at 2 – 8°C recommended). Further diluted in saline shelf life 6 hours.	Each 2 mg vial contains 2 mg mitomycin and 4 mg mannitol. Each 10 mg vial contains 10 mg mitomycin and 20 mg mannitol. Each 20 mg vial contains 20 mg mitomycin and 40 mg mannitol.	Each vial contains either mitomycin 2 mg, mitomycin 10 mg or mitomycin 20 mg. To administer add Sterile Water for injection 4 mL to the 2 mg vial, or 20 mL to the 10 mg and 20 mg vials. Shake to dissolve.	Reconstituted with water for injection (mitomycin concentration 0.5 mg/mL to 1 mg/mL), it is stable for 24 hours stored in a refrigerator (2 – 8°C) and protected from light.

Manufacturer	SmPC shelf life	Excipients / formulation details	Other comments	Shelf-life recommendation
Accord (for Canadian market)	Reconstituted with Sterile Water for Injection to a concentration of 0.5 mg / mL, mitomycin is stable for 72 hours refrigerated or 6 hours at controlled room temperature (15° - 30°C), protected from light. Reconstituted solutions may be further diluted with Sodium Chloride 0.9% and between 20 to 40 micrograms per mL: shelf life 18 hours	Each vial contains mitomycin 20 mg and mannitol 40 mg.	To reconstitute a vial of mitomycin, add Sterile Water for Injection 40ml to 20mg vial	Reconstituted with Sterile Water for Injection to a concentration of 0.5 mg / mL, mitomycin is stable for 72 hours refrigerated at 2 – 8°C Reconstituted in Water for Injection and diluted in Sodium Chloride 0.9% to between 20 to 40 micrograms per mL: 18 hours stored in a refrigerator (2 – 8°C)
Kyowa PL16508/0042-0045	After reconstitution, the solution is chemically and physically stable for 24 hours when protected from light and stored in a cool place. Do not refrigerate.	Powder for solution for infusion Sodium Chloride	The contents of the vial should be reconstituted with Water for Injection or saline, at least 5 ml for the 2 mg, at least 10 ml for the 10 mg, at least 20 ml for the 20 mg and at least 40 ml for the 40 mg vial. If possible, avoid mixing with other low pH injectable solutions.	Reconstituted solution 24 hours stored in a cool place (non-refrigerated)

Manufacturer	SmPC shelf life	Excipients / formulation details	Other comments	Shelf-life recommendation
Medac (intravesical use) PL 11587/0090 (40mg)	After reconstitution the medicinal product should be used immediately.	Powder for solution for intravesical use: Urea. Solvent for intravesical solution: Sodium chloride and water for injections.	Dissolve the content of one vial of Mitomycin medac (equivalent to 40 mg mitomycin) in 40 ml sterile sodium chloride 9 mg/ml (0.9 %) solution for injection.	Use immediately
Vygoris Limited PL 47587/0001	The chemical and physical stability at room temperature and during exposure to light of a reconstituted solution is 1 hour with Water for Injections 2 hours with sodium chloride 9 mg/ml (0.9%) solution All reconstituted solutions are intended for immediate use	Powder for solution for injection/infusion or intravesical use Mannitol, 36% hydrochloric acid and sodium hydroxide for pH adjustment. Each vial contains mitomycin 20 mg and mannitol 40 mg[3].	In intravesical therapy, 20 - 40 mg of mitomycin, corresponding to 1 - 2 vials of Mitocin 20 mg in 20 - 40 ml of water for injections or sodium chloride (0.9%) Solution. Preparation of ready-to-use solution for injection or infusion. The contents of one vial of Mitocin 20 mg are dissolved in 40 ml of water for injections by swirling. For intravenous infusion the solution of Mitocin 20 mg can be diluted in 40 ml of water for injections with isotonic sodium chloride infusion solution down to a concentration of 20 - 40 micrograms of mitomycin/ml.	Use within 2 hours in 0.9% sodium chloride but see also below.

Conclusions (based on the data above)

Mitomycin is a naturally derived product and hence may show some variation in terms of impurity profiles etc. however, this is well controlled within the pharmacopoeias for the starting material. The Vygoris product has the same excipients in the same relative concentrations[3] as the Accord products but the formulations from the other two suppliers are different from each other and the Accord and Vygoris products, it is recommended that data is not extrapolated between the three formulations.

All of the Accord products for the various markets appear to be identical in formulation having a 1:2 Mitomycin to Mannitol ratio and no other excipients. Despite this the reconstitution directions are totally different for the different markets using reconstitution with Sodium Chloride 0.9% for the UK products but using Water for Injection for the USA, Australia and Canadian markets. The Vygoris product contains the same ratio of mitomycin to mannitol although it does also mention pH adjustment, this does allow for reconstitution with either Sodium Chloride 0.9% or Water for Injection for intravesical use but states water for injection as the initial diluent for intravenous use.

The in-use shelf life for the Accord products also varies significantly between the markets with the UK product stating to use immediately, the US product has a shelf life of 14 days refrigerated for the reconstituted solution although this is reduced to 12 hours on further dilution in Sodium Chloride 0.9%. The Australian product can be assigned a shelf life of 24 hours stored in a refrigerator (2 – 8°C) and protected from light between 0.5 mg/mL and 1 mg/ml, this is reduced to six hours on further dilution in Sodium Chloride 0.9%. The Canadian product reconstituted with Sterile Water for Injection to a concentration of 0.5 mg / mL mitomycin is stable for 72 hours refrigerated at 2 – 8°C, reduced to 18 hours on further dilution with Sodium Chloride 0.9%.

The Vygoris product states that the shelf life at room temperature and during exposure to light of a reconstituted solution is 1 hour with Water for Injections 2 hours with Sodium chloride 0.9%, the data behind this statement was supplied on request[4]. The data does indicate that the decision to assign this shelf life was robustly made. For Mitomycin 20mg dissolved in Water for Injection to a concentration of 0.5 mg/ml stored at 25°C without light protection the shelf life was limited by the levels of degradation product albomitomycin (Impurity D) which was out of specification after 2 hours, the active drug remained above 98% of starting concentration at 4 hours. For Mitomycin 20mg dissolved in the instillation set in Sodium Chloride 0.9% to a concentration of 1.0 mg/ml when stored at 25°C without light protection then the degradation rate measured by loss of active was faster, limiting the shelf life to 2 hours although in this case levels of albomitomycin (Impurity D) did not exceed the manufacturers limit until the 12 hour time point.

This is an interesting reinforcement of the fact that the degradation profile is inconsistent and highly pH dependant but it is in-line with the Accord international advice that the product is more stable (from the loss of active viewpoint alone) in Water for Injections. Working out the degradation rate in

Sodium Chloride 0.9% and applying Arrhenius equation would give a refrigerated shelf life (5°C) of 11.8 hours based on the average degradation rate and 9 hours based on the highest degradation rate (6 hour time point). The rate of loss of active is lower in Water for Injection however, the appearance of albomitomycin (Impurity D) to just below limits at 1 hour makes extrapolation of this data unsafe.

Published Papers

There are limited published studies of Mitomycin stability of any quality, the following two papers are of interest.

Stability of Reconstituted and Diluted Mitomycin C Solutions in Polypropylene Syringes and Glass Vials; Pharmaceutical Technology in Hospital Pharmacy;1,2:83-89 2016; Briot T, Truffaut C, Le Quay L, Lebreton A, Lagarce F.[5]

A stability indicating HPLC-UV method was developed and validated according to the ICH guidelines. Concentrations of the Mitomycin C stored at 25 °C and 60 % of relative humidity and protected from light in polypropylene syringes (1 mg/mL and 0.2 mg/mL) or glass vials (1 mg/mL). Mitomycin C stability was demonstrated in syringes and glass vials at 1 mg/mL only for 8 hours in water for injections and for 10 hours at 0.2 mg/mL in 0.9 % sodium chloride solutions (based on loss of 10% of active). After 96 hours the relative concentrations were found below 80 % as compared to initial concentrations, degradation products remained below 3%.

The Degradation of Mitomycin C Under Various Storage Methods; J Glaucoma; 25, 6: 477-481. 2016; Kinast R.M, Akula K.K, DeBarber A.E, Barker G.T, Gardiner S.K, Whitson E, Mansberger S.L.[6]

Used reversed-phase high-performance liquid chromatography to determine the stability of 0.4 mg/mL Mitomycin C solutions, and liquid chromatography-electrospray ionization-mass spectrometry to identify degradation products. The paper compared stability after different storage conditions but did not look at the stability profile during these conditions. These included refrigerated for one or two weeks, frozen for 23 days and transported in ice. They tested 3 samples for each storage method when samples reached room temperature (time 0), and then 1, 4, and 24 hours later. All products were within specification after the initial storage period but showed significant degradation over 24 hours at room temperature. They also identified small amounts (<3.2%) of 2 degradants, cis-hydroxymitosene and trans-hydroxymitosene, across all samples. The study used Mitosol (Mobius Therapeutics LLC) which contains 0.2mg of mitomycin and mannitol in a 1:2 concentration ratio and according to product information should be used within one hour of reconstitution.

Mitomycin injection is very sensitive to pH in terms of drug stability and the greatest stability in aqueous solution is at a pH 7-8. Mitomycin degrades rapidly below that pH and also at higher pH, although the degradation mechanisms are different for acidic and basic conditions[7]. The pH of water for injection and Sodium Chloride 0.9% are likely to be similar but not necessarily the same and the diluent presentation and final product containers may influence the final product pH.

Advice for use of the UK Accord Product

Any change to what is stated in the UK SmPC will mean that usage is outside of the licensed use, however, following the 'use immediately' advice is not practical where preparation is necessarily within pharmacy aseptic units and hence remote from the patient. A pragmatic approach would be to follow the SmPC in terms of reconstituting with Sodium Chloride 0.9% and it would be safe to assign a 12-hour shelf life with the product being stored in a refrigerator (2 – 8°C) ahead of use. This shelf life could also be applied when Mitomycin is further diluted in Sodium Chloride 0.9% in the concentration range 20 micrograms/ml to 1mg/ml. Note that the product must be refrigerated as soon as possible following reconstitution ideally within 30 minutes.

Alternatively, and bearing in mind the formulations for the US, Australian and Canadian Accord products appear to be identical to the UK licensed product reconstitution with water for injection (although expressly forbidden within the UK SmPC) would yield a solution which would appear to be stable for at least 24 hours at 0.5 – 1mg/ml stored in a refrigerator. Although some statements and studies do show that a longer shelf life should be possible the expected variations in pH may impact on this, also the levels of albomitomycin (Impurity D) are likely to be borderline, and hence extending beyond 24 hours is not recommended. Once more the product must be refrigerated as soon as possible following reconstitution ideally within 30 minutes. Note that the 40mg Accord product (PL 20075/0515) should only be reconstituted to 0.5mg/ml in accordance with the SmPC, this is due to concerns with the sub-visible particle levels of the 1mg/ml solution for this vial size[8].

Advice for use of the UK Vygoris Product

The SmPC suggests reconstitution with water for injection although this is associated with only a one-hour shelf life which is not practical for aseptic services preparation. The formulation is identical to the Accord product and, for intravesical use can be reconstituted with water or saline, the reason why water for injection is stated is not clear and the low osmolarity of the product itself would suggest that it could equally be reconstituted with sodium chloride 0.9%, in either case the 12-hour shelf life discussed above can safely be assigned with the product being stored in a refrigerator (2 – 8°C) ahead of use. This shelf life can also be applied when Mitomycin is further diluted in Sodium Chloride 0.9% in the concentration range 20 micrograms/ml up to 1mg/ml. Note that the product must be refrigerated as soon as possible following reconstitution ideally within 30 minutes.

There is a study[7] of the stability of Mitomycin buffered with a phosphate buffer at pH 7.4 for use as eye drops which was used to evidence that at this pH the drug can be assigned a shelf life of 42 days at 2 – 8°C at 0.2 – 0.4mg/ml, this was carried out using the Kyowa brand / formulation of Mitomycin but does further evidence the criticality of pH on the drug stability.

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Changes from previous version

Clarified shelf life for the Vygoris brand to include both 0.9% Sodium Chloride and Water for Injection as reconstituting solvents.

References

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8. Personal communication from Accord AUK20-004441 EN Mitomcyin 21st August 2020