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3.2.P.1 Description and Composition of the Drug Product Table 1: Weight composition of ^{123}I - mIBG final solution, 0.74 GBq (20 mCi) in 10 g (density 1.011 g/ml) <table> Vial: 10 ml, Type 1 pharmaceutical glass (Ph.Eur.), steam-sterilized Rubber Septum: Grey rubber closure, partially coated with Teflon, type 1241/PH 4104/40 Manufacturer: The West Company France S.A., Le Nouvion-en-Thiérache, France Distributor: Aluglas After dispensing vials are closed with the rubber septum and a metal cap. The colour of the metal cap is different for each product, produced by GE Healthcare B.V. (^{123}I-metaiodobenzylguanidine = red). For shipment vials are placed in a lead container.	**3.2.P.1 Description and Composition of the Drug Product** Table 1: Weight composition of ^{123}I - mIBG final solution, 0.74 GBq (20 mCi) in 10 g (density 1.011 g/ml) <table> Vial: 10 ml, Type 1 pharmaceutical glass (Ph.Eur.), sterilized Rubber Septum: Grey rubber closure, partially coated with Teflon, type 1241/PH 4104/40 After dispensing vials are closed with the rubber septum and a metal cap. The colour of the metal cap is different for each product, produced by GE Healthcare B.V. (^{123}I-metaiodobenzylguanidine = red). For shipment vials are placed in a lead container.

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3.2.P.3.1 Manufacturer(s) GE Healthcare B.V. Den Dolech 2 5612 AZ Eindhoven The Netherlands	**3.2.P.3.1 Manufacturer(s)** **Site of manufacture, quality control testing and batch release** GE Healthcare B.V. Den Dolech 2 NL-5612 AZ Eindhoven The Netherlands **Sites of container closure preparation** Washing and sterilising of the vials and closures is performed by: GE Healthcare Limited, Corolin Road, Lower Tuffley Lane Gloucester, GL2 5DQ, UK
3.2.P.3.3 Description of Manufacturing Process and Process Controls <Figure> **Figure 1: Schematic description of the manufacturing process of AdreView, Iobenguane (^{123}I Injection)**	**3.2.P.3.3 Description of Manufacturing Process and Process Controls** <Figure> **Figure 1: Schematic description of the manufacturing process of AdreView, Iobenguane (^{123}I Injection)** **1. Preparation of the Bulk solution** *Text regarding the preparation of the bulk solution has been moved from 3.2.P.3.4 to this section since it is more appropriate to state this information here.* **2. Dispensing of the Bulk Solution** *Text regarding the dispensing of the bulk solution has been moved from 3.2.P.3.4 to this section since it is more appropriate to state this information here.* **3. Terminal Sterilisation** *Text regarding the terminal sterilisation has been moved from 3.2.P.3.4 to this section since it is more appropriate to state this information here.*

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	4. Container Preparation 4.1 Vials The vials and closures are prepared by: GE Healthcare Limited, Corolin Road, Lower Tuffley Lane Gloucester, GL2 5DQ, UK The vials are washed with Water for Injections. After washing, the vials are placed in tins metal containers). These tins hold the vials during the sterilisation / depyrogenation cycle in an oven. The depyrogenated vials are then unloaded from the tins into the vial/stopper assembly unit in a Grade A area. 4.2 Closures The closures are received from the manufacturer pre-washed with Water for Injections and pre- packed in a Grade A area in bags suitable for steam sterilisation. Bags containing the closures are steam sterilised by autoclaving at 121°C for not less than 15 minutes, prior to introduction to the vial/stopper assembly unit. The sterilised stoppers are placed onto the sterilised vials in a Grade A area. After this process step the closed vials are unloaded and placed in sterilised tins. These tins are closed with a metal lid and double packed in sterilised plastic bags for transport back to GE Healthcare BV for acceptance testing and storage before use. 4.3 Overseals The overseals are sterilised by exposure to gamma irradiation by a contracting company. The overseals, packaged in protective primary and secondary packs, are sterilised by gamma irradiation in accordance with *EN 552 Sterilization of medical devices-Validation and routine control of sterilization by irradiation* and *ISO 11137 Sterilization of health care products -Requirements for validation and routine control - Radiation sterilization*.. After sterilisation, the overseals are transported back to GE Healthcare BV for acceptance testing and storage before use.

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3.2.P.3.4 Controls of Critical Steps and Intermediates **Prepararing of the Bulk solution** *Text regarding the preparation of the bulk solution has been moved to 3.2.P.3.3 since it is more appropriate to state this information there.* pH Specification: 5.0-6.5 Method: pH is determined potentiometrically Osmolality Specification: 350-450 milliOsmol/kg Method: Osmolality is determined using a Semi-Micro-osmometer. The calibration of this instrument is checked twice per month, using water (0 milliOsmol/kg), a home-made reference solution (400 milliOsmol/kg) and a reference-solution (300 milliOsmol/kg), obtained from Gonotec GmbH, Berlin. If necessary the osmometer is adjusted. The intermediate solution must be dispensed and sterilised within 4 hours after EOC (End of Chemistry). During that time the solution should be stored at 15-25°C. **Dispensing of the Bulk solution** *Part of the text regarding the dispensing of the bulk solution has been moved to 3.2.P.3.3 since it is more appropriate to state this information there.* The vials are visually examined for the absence of particles using polarized light. Vials meet specification if there are no visible particles. **Autoclavation** *Part of the text regarding the autoclavation of the bulk solution has been moved to 3.2.P.3.3 since it is more appropriate to state this information there.* The vials are autoclaved for 15 min. at 1.1 atm pressure difference and 121°C.	**3.2.P.3.4 Controls of Critical Steps and Intermediates** There are no intermediates isolated during manufacture of AdreView. The following controls are applied to the bulk product, prior to dispensing, and are reported against the finished product specification in the batch analysis data. pH Specification: 5.0-6.5 Method: pH is determined potentiometrically Osmolality Specification: 350-450 milliOsmol/kg Method: Osmolality is determined using a Semi-Micro-osmometer. The calibration of this instrument is checked twice per month, using water (0 milliOsmol/kg), a home-made reference solution (400 milliOsmol/kg) and a reference-solution (300 milliOsmol/kg), obtained from Gonotec GmbH, Berlin. If necessary the osmometer is adjusted. The intermediate solution must be dispensed and sterilised within 4 hours after EOC (End of Chemistry). During that time the solution should be stored at 15-25°C. **Dispensing of the Bulk Solution** The integrity of the filter is checked using the bubble-point test (Specification > 3 bar). The vials are visually examined for the absence of particles using polarized light. Vials meet specification if there are no visible particles. **Sterilisation** The vials are autoclaved for 15 min. at 1.1 atm pressure difference and 121°C.

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3.2.P.3.5 Process Validation and/or Evaluation ..... **2 Preparation of Vials, Closures and Overseals** Information on the acceptance testing of the vials, closures and overseals used in the primary containment system is given in 3.2.P.7 and details of their preparation are given in 3.2.P.3.3. The vials are first pre-washed in dilute hydrochloric acid (analytical reagent grade) to remove surface impurities which might interact with the product solution. After this, the vials are machined washed with water (Water for Injections) and then unloaded into an LFU and double-packed into steam-penetrable packs. The sealing device used to seal the packs is checked at prescribed intervals to demonstrate continuing efficacy. After sealing, the packs are transferred to an autoclave sited within the Helmond facility and sterilised, along with a sterilisation indicator, by autoclaving at 121°C for at least 15 minutes. The autoclave is validated in accordance with Dutch Regulation R6103 and subject to re-validation at prescribed intervals. The autoclave is also validated against the specific load of vials. After unload, the sterilisation indicator is checked to ensure that the correct colour change has occurred and the packs are checked individually to ensure the integrity of the seals. The sterilised packs of vials are packed into protective bags prior to shipment to GE Healthcare BV. The closures are manufactured by the West Company and supplied already washed. However, in addition to this, the closures undergo further washing at the Helmond facility to ensure freedom from particulate contamination. This involves rinsing three times with 0.22 µm filtered Water for Injections Ph. Eur. in a laminar flow unit. After manual washing, the closures are packed into steam-sterilisable packs and sterilised by autoclaving at 121°C for not less than 15 minutes. After unload, the sterilisation indicator is checked to ensure that the correct colour change has occurred and the packs are checked individually to ensure the integrity of the pack seals. The controls exercised over the autoclave are the same as for the vials. Information on the efficacy of the washing process and bioburden levels prior to sterilisation is given in the attached report, *`DP008R: 040 - Bioburden Levels on Vials and Closures Prior to Sterilisation `*. The efficacy of the wash process was assessed by measuring bioburden levels on closures and vials before and after the wash process. The results obtained were satisfactory with bioburden levels of less than 1 cfu for both vials and closures prior to sterilisation. In order to validate the efficacy of endotoxin removal, vials and closures were `spiked` with endotoxins and then re-tested after the wash process. Details of the work carried out and the results obtained are given in the attached report, *`DP008R: 064 – Efficacy of Wash Process for Vials and Closures: Reduction of Endotoxin Content`*. The results demonstrate that the wash process achieves a 103 reduction in endotoxin levels. Refer to reports: *- DP008R: 040 - Bioburden Levels on Vials and Closures Prior to Sterilisation.* *- DP008R: 064 – Efficacy of Wash Process for Vials and Closures: Reduction of Endotoxin Content* - Dutch Regulation R6103 is not available in English but English translation is provided.	**3.2.P.3.5 Process Validation and/or Evaluation** ..... **2 Preparation of Vials, Closures and Overseals** Information on the acceptance testing of the vials, closures and overseals used in the primary containment system is given in 3.2.P.7 and details of their preparation are given in 3.2.P.3.3. **2.1 Vials and Closures** Refer to reports: *DP008R: 040 - Bioburden Levels on Vials and Closures Prior to Sterilisation.* **(a) Vials** The following validation studies were carried out to support the depyrogenation of vials at Gloucester. • thermometric mapping, over 9 runs with each test position being evaluated in triplicate, with full oven load of 95 tins filled with 10ml vials plus load probe tin. • Endotoxin challenge, carried out in three runs, of identified cold spots derived from the thermometric evaluation results, within a full oven load of 95 tins filled with 10ml vials plus load probe tin. **(i) Acceptance criteria** • All thermocouples to attain a minimum of 200°C for a minimum of 2 hours. • All Endotoxins must show a 3 log reduction. **(ii) Results** All thermocouples attained a minimum of 200°C for a minimum of 2 hours. All endotoxins were within specification with a 3 log reduction. **(b) Closures** The closures are supplied already washed. They are packed into steam-sterilisable packs and sterilised by autoclaving at 121°C for not less than 15 minutes. After unload, the sterilisation indicator is checked to ensure that the correct colour change has occurred and the packs are checked individually to ensure the integrity of the pack seals. Performance Qualification has been carried out to show that the closure sterilisation cycle developed on the autoclave, is capable of effectively sterilising the closures used for AdreView, by demonstrating it will effectively sterilise stoppers inoculated with a spore suspension of *Geobacillus stearothermophilus* with a population of greater than 10^6 per stopper and a D_{121}Value of greater than 1.5 minutes. A D-value and population determination study was performed. The results are summarised in **Errore. L'origine riferimento non è stata trovata.**2. <table 2> **Table 2: Summary of D-value testing on stoppers** Maximum loads of 12000 stoppers were used during this qualification. Each maximum load was divided into four lots, triple wrapped in autoclave bags. The inoculated stoppers were placed in two bags that were considered to be the worst case positions in the load during Cycle Development.

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The overseals, packaged in protective primary and secondary packs, are sterilised by gamma irradiation in accordance with *EN 552 Sterilization of medical devices-Validation and routine control of sterilization by irradiation* and *ISO 11137 Sterilization of health care products - Requirements for validation and routine control - Radiation sterilization*. Dosemapping data are provided in Report CY QA08042 which demonstrate that an adequate irradiation dose is delivered throughout the load.	The remaining 2 bags contained thermocouples. The total amount of thermocouples and inoculated stoppers in each maximum load is summarised in 3 below. <table 3> **Table 3 Stoppers Load Presentation, Thermocouple and Biological Indicator Requirements** The bags were sterilised by autoclaving for 50 mins at a control temperature of 122.5°C. After autoclaving, the stoppers were incubated at 55-60ºC for seven days. **Study acceptance criteria** The stoppers inoculated with *Geobacillus stearothermophilus* located in the load must show no growth after 7 days incubation at 55 - 60°C. The Biological Indicators used as positive controls must show growth after 7 days incubation. **Results** The study has shown that stopper loads achieve a 6 log reduction of microorganisms 2.2 Overseals The overseals, packaged in protective primary and secondary packs, are sterilised by gamma irradiation in accordance with *EN 552 Sterilization of medical devices-Validation and routine control of sterilization by irradiation* and *ISO 11137 Sterilization of health care products -Requirements for validation and routine control - Radiation sterilization*. A dose mapping study, performed by the sterilising company, has demonstrated that an adequate irradiation dose is delivered throughout the load. **3 Dispensing of the Bulk Solution** **…..**

relativamente alla specialità medicinale indicata in oggetto e alle confezioni sotto elencate:

038979011 «74 mbq/ml soluzione iniettabile» 1 flaconcino da 10 ml -ogni flaconcino può contenere da 37 a 740 mbq.

I lotti già prodotti possono essere mantenuti in commercio fino alla data di scadenza indicata in etichetta.

La presente determinazione ha effetto dal giorno successivo a quello della sua pubblicazione nella *Gazzetta Ufficiale* della Repubblica italiana.

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