Iohexol Injection

DEFINITION

Iohexol Injection is a sterile solution of Iohexol in Water for Injection. It contains NLT 95.0% and NMT 105.0% of the labeled amount of iohexol ($C_{19}H_{26}I_3N_3O_9$) as organically bound iodine. It may contain small amounts of suitable buffers and Edetate Calcium Disodium as a stabilizer. Iohexol Injection intended for intravascular or intrathecal use contains no antimicrobial agents.

IDENTIFICATION

Delete the following:

▲• **A. PROCEDURE**
Analysis: Evaporate 1 mL of Injection to dryness, and heat the residue so obtained in a crucible.
Acceptance criteria: Violet vapors are evolved.▲*USP34*

Delete the following:

▲• **B. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST ⟨201⟩**
Standard solution: 10 mg/mL in methanol
Sample solution: 10 mg/mL in methanol
Developing solvent system: *n*-Butyl alcohol, water, and glacial acetic acid (50:25:11)
Analysis
Samples: *Standard solution* and *Sample solution*
Develop the chromatogram, and locate the spots by short-wavelength UV light.▲*USP34*

Add the following:

▲• **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *System suitability solution*, as obtained in the test for *Organic Impurities*.▲*USP34*

ASSAY

• **PROCEDURE**
Sample: A volume of Injection equivalent to 300 mg of iodine
Analysis: Transfer the *Sample* to a glass-stoppered, 250-mL conical flask. Add 25 mL of 1.25 N sodium hydroxide and 500 mg of powdered zinc, connect the flask to a reflux condenser, and reflux the solution for 1 h. Cool the flask to room temperature, rinse the condenser with 20 mL of water, disconnect the flask from the condenser, and filter the mixture. Rinse the flask and the filter thoroughly with small portions of water, adding the rinsings to the filtrate. Add 5 mL of glacial acetic acid, and titrate with 0.1 N silver nitrate VS. Each mL of 0.1 N silver nitrate is equivalent to 27.37 mg of $C_{19}H_{26}I_3N_3O_9$.
Acceptance criteria: 95.0%–105.0%

IMPURITIES

Delete the following:

▲**Inorganic Impurities**
• **HEAVY METALS,** *Method I* ⟨**231**⟩**:** NMT 20 ppm▲*USP34*
• **ORGANIC IMPURITIES**
Solution A: Acetonitrile
Solution B: Water
Mobile phase: The percentage of *Solution A* increases from 1% to 13% at a rate of 0.2%/min.
System suitability solution: 1.5 mg/mL, 0.0075 mg/mL, and 0.0069 mg/mL each of USP Iohexol RS, USP Iohexol Related Compound A RS, and USP Iohexol Related Compound C RS in water
Sample solution: 1.5 mg/mL of Iohexol
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 25-cm stainless steel column; packing L1
Flow rate: 1.0 mL/min
Injection volume: 10 µL
System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times for the *exo*-isomer of iohexol and the *O*-alkylated compounds are 1.0 and between 1.1 and 1.4, respectively.]
[NOTE—The peak area of iohexol related compound C is 0.5% ± 0.1% compared to the total area of all the peaks in the chromatogram.]
Suitability requirements
Resolution: NLT 20.0 between iohexol related compound A and iohexol related compound C
Analysis
Sample: *Sample solution*
Excluding peaks with retention times between 0.84 (relative to the *endo*-isomer of iohexol, which is the first main peak) and 1.0, calculate the percentage of *O*-alkylated compounds and any other individual impurity peak, in the portion of Iohexol taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of each impurity
r_T = sum of all the peak responses
Acceptance criteria
Individual impurity: NMT 0.6% of *O*-alkylated compounds; NMT 0.1% of any other individual impurity
Total impurities: NMT 0.3 %, excluding *O*-alkylated compounds

SPECIFIC TESTS

• **BACTERIAL ENDOTOXINS TEST ⟨85⟩:** NMT 0.2 USP Endotoxin Unit per 50 mg of iodine
• **pH ⟨791⟩:** 6.8–7.7
• **PARTICULATE MATTER IN INJECTIONS ⟨788⟩:** The Injection labeled for intrathecal use meets the requirements for small-volume injections.
• **FREE IODIDE:** Transfer 5.0 mL of Injection to a suitable container, add 20 mL of water, and titrate with 0.001 N silver nitrate VS using a silver electrode in combination with an appropriate reference electrode. Each mL of 0.001 N silver nitrate is equivalent to 0.1269 mg of iodine.
Acceptance criteria: NMT 0.02%, based on the content of iohexol
• **INJECTIONS ⟨1⟩:** Meets the requirements

ADDITIONAL REQUIREMENTS

Change to read:

• **PACKAGING AND STORAGE:** Preserve Injection intended for intravascular or intrathecal use in single-dose ●or multiple-dose plastic or Type I glass containers. Store at controlled room temperature, protected from light. Do not freeze.● (RB 1-Sep-2011)

Change to read:

• **LABELING:** Label containers of Injection to direct the user to discard any unused portion. The labeling states also that it is not to be used if it is discolored or contains a precipitate. Label it also to state its routes of administration. •When the specific dose strength is not intended for intrathecal use, label it to indicate "serious injury can occur if given by intrathecal route".• (RB 1-Sep-2011)

• **USP REFERENCE STANDARDS** ⟨**11**⟩

USP Endotoxin RS
USP Iohexol RS
USP Iohexol Related Compound A RS
5-(Acetylamino)-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide.
USP Iohexol Related Compound C RS
N,*N*′-Bis(2,3-dihydroxypropyl)-5-nitro-1,3-benzenedicarboxamide.