

with 0.1 mol/L ammonium thiocyanate VS (indicator: 5 mL of ammonium iron (III) sulfate TS). Perform a blank determination.

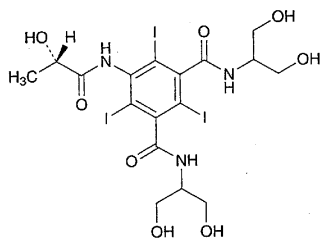
Each mL of 0.1 mol/L silver nitrate VS  
= 13.124 mg of  $\text{CHI}_3$

**Containers and storage** Containers—Tight containers.

Storage—Light-resistant.

## Iopamidol

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$\text{C}_{17}\text{H}_{22}\text{I}_3\text{N}_3\text{O}_8$ : 777.09

*N,N'*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2*S*)-2-hydroxypropanoylamino]-2,4,6-triiodoisophthalamide [62883-00-5]

Iopamidol, when dried, contains not less than 99.0% of  $\text{C}_{17}\text{H}_{22}\text{I}_3\text{N}_3\text{O}_8$ .

**Description** Iopamidol occurs as a white crystalline powder.

It is very soluble in water, sparingly soluble in methanol, and very slightly soluble in ethanol (99.5).

**Identification (1)** To 0.05 g of Iopamidol add 5 mL of hydrochloric acid, heat for 10 minutes in a water bath: the test solution responds to the Qualitative Tests for primary aromatic amines.

(2) Heat 0.1 g of Iopamidol over a flame: a purple gas is evolved.

(3) Determine the infrared absorption spectrum of Iopamidol, previously dried, as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

**Optical rotation**  $[\alpha]_{436}^{20}$ :  $-4.6$  –  $-5.2^\circ$  (after drying, 4 g, water, warm, after cooling, 10 mL, 100 mm).

**Purity (1)** Clarity and color of solution—Dissolve 1.0 g of Iopamidol in 10 mL of water: the solution is clear and colorless.

(2) Primary aromatic amines—Dissolve 0.60 g of Iopamidol in 8 mL of water, add 1 mL of a solution of sodium nitrite (1 in 50) and 12 mL of 2 mol/L hydrochloric acid TS, shake, and allow to stand for 2 minutes. Add 1 mL of a solution of ammonium amidosulfate (1 in 10), shake well, allow to stand for 1 minute, and add 1 mL of naphthylethylenediamine TS and water to make exactly 50 mL. Determine the absorbance of this solution at 495 nm using a solution, prepared in the same manner, as the blank:

the absorbance is not more than 0.12 (not more than 0.020%).

(3) Iodine—Dissolve 2.0 g of Iopamidol in 25 mL of water, add 5 mL of 1 mol/L sulfuric acid and 5 mL of toluene, shake well, and allow to stand: the toluene layer is colorless.

(4) Free iodine ion—Weigh accurately about 5.0 g of Iopamidol, dissolve in 70 mL of water, and adjust the pH to about 4.5 with dilute acetic acid. To this solution add 2 mL of 0.1 mol/L sodium chloride TS, and titrate with 0.001 mol/L silver nitrate VS (potentiometric titration).

Each mL of 0.001 mol/L silver nitrate VS  
= 0.12690 mg of I

Content of iodine ion in Iopamidol is not more than 0.001%.

(5) Heavy metals—Moisten 1.0 g of Iopamidol with a small quantity of sulfuric acid, heat gradually to almost incinerate by a possibly lower temperature. After cooling, moisten again with a small quantity of sulfuric acid, heat gradually until white fumes no longer are evolved, and incinerate by ignition between 450 to 550°C. Proceed as directed in Method 2, and perform the test. Prepare the control solution with 1.0 mL of Standard Lead Solution (not more than 10 ppm).

(6) Related substances—Dissolve 0.10 g of Iopamidol in water to make exactly 10 mL, and use this solution as the sample solution. Separately, dissolve 0.010 g of *N,N'*-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-hydroxyacetylaminio-2,4,6-triiodoisophthalamide in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20  $\mu\text{L}$  each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine each peak area of the both solutions by the automatic integration method: each area of the peaks other than the peak of Iopamidol from the sample solution is not larger than the peak area of the standard solution, and the total of these areas is not larger than 2.5 times of the peak area of the standard solution.

**Operating conditions—**

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column 4 mm in inside diameter and 25 cm in length, packed with octadecylsilylated silica gel for liquid chromatography (5  $\mu\text{m}$  in particle diameter).

Column temperature: A constant temperature of about 35°C.

Mobile phase: Use water as the mobile phase A, and a mixture of water and methanol (3:1) as the mobile phase B. Change the mixed ratios of the mobile phase A and the mobile phase B stepwise as follows:

Time after injection of sample (min)	Mobile phase A (%)	Mobile phase B (%)
0 – 6	92	8
6 – 18	92 → 65	8 → 35
18 – 30	65 → 8	35 → 92
30 – 34	8	92

Flow rate: Adjust the flow rate to 1.5 mL per minute.

Time span of measurement: About 4.3 times as long as the retention time of iopamidol.

System suitability—

System performance: Dissolve 1 mL of the sample solution and 0.010 g of *N,N'*-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-hydroxyacetyl-amino-2,4,6-triiodoisophthalamide in water to make 100 mL. When the procedure is run with 20  $\mu$ L of this solution under the above operating conditions, *N,N'*-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-hydroxyacetyl-amino-2,4,6-triiodoisophthalamide and iopamidol are eluted in this order with the resolution between these peaks being not less than 7.

System repeatability: When the test is repeated 6 times with 20  $\mu$ L of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of *N,N'*-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-hydroxyacetyl-amino-2,4,6-triiodoisophthalamide is not more than 1.0%.

**Loss on drying** Not more than 0.30% (1 g, 105°C, 3 hours).

**Residue on ignition** Not more than 0.10% (1 g).

**Assay** Weigh accurately about 0.5 g of Iopamidol, previously dried, transfer to a saponification flask, dissolve in 40 mL of sodium hydroxide TS, add 1 g of zinc powder, boil for 30 minutes under a reflux condenser, cool, and filter. Wash the flask and the filter paper with 50 mL of water, and combine the washing with the filtrate. Add 5 mL of acetic acid (100) to this solution, and titrate with 0.1 mol/L silver nitrate VS (potentiometric titration).

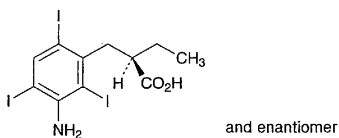
Each mL of 0.1 mol/L silver nitrate VS  
= 25.903 mg of  $C_{17}H_{22}I_3N_3O_8$

**Containers and storage** Containers—Well-closed containers.

Storage—Light-resistant.

## Iopanoic Acid

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$C_{11}H_{12}I_3NO_2$ : 570.93  
(*RS*)-2-(3-Amino-2,4,6-triiodobenzyl)butanoic acid  
[96-83-3]

Iopanoic Acid, when dried, contains not less than 98.0% of  $C_{11}H_{12}I_3NO_2$ .

**Description** Iopanoic Acid occurs as a light yellowish white, crystalline powder. It has a faint, characteristic odor.

It is soluble in ethanol (95) and in acetone, sparingly soluble in acetic acid (100) and in diethyl ether, and practically insoluble in water.

It dissolves in sodium hydroxide TS.

It is gradually colored by light.

**Identification (1)** Heat 0.1 g of Iopanoic Acid over a flame: a purple gas is evolved.

(2) Determine the infrared absorption spectrum of Iopanoic Acid, previously dried, as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

**Melting point** 152 – 158°C (with decomposition).

**Purity (1)** Soluble halides—Dissolve 2.5 g of Iopanoic Acid in 20 mL of water and 2.5 mL of ammonia TS, and add 20 mL of dilute nitric acid and water to make 100 mL. Allow the mixture to stand for 15 minutes with occasional shaking, and filter. Discard the first 10-mL portion of the filtrate, transfer the subsequent 25 mL of the filtrate to a Nessler tube, and add ethanol (95) to make 50 mL. Proceed as directed in the Chloride Limit Test using this solution as the test solution. Prepare the control solution as follows: to 0.10 mL of 0.01 mol/L hydrochloric acid VS add 6 mL of dilute nitric acid and water to make 25 mL, then add ethanol (95) to make 50 mL.

(2) Iodine—Dissolve 0.20 g of iopanoic Acid in 2.0 mL of sodium hydroxide TS, and 2.5 mL of 0.5 mol/L sulfuric acid TS, and allow to stand for 10 minutes with occasional shaking. Add 5 mL of chloroform, shake vigorously, and allow to stand: the chloroform layer remains colorless.

(3) Heavy metals—Proceed with 1.0 g of Iopanoic Acid according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(4) Arsenic—Prepare the test solution with 1.0 g of Iopanoic Acid according to Method 3, and perform the test using Apparatus B (not more than 2 ppm).

**Loss on drying** Not more than 0.5% (1 g, 105°C, 2 hours).

**Residue on ignition** Not more than 0.10% (1 g).

**Assay** Weigh accurately about 0.4 g of Iopanoic Acid, previously dried, and add 1 g of zinc powder and 10 mL of acetic acid (100). Boil for 30 minutes under a reflux condenser, add 30 mL of water through the condenser, and filter through absorbent cotton. Wash the flask and the cotton with two 20-mL portions of water, and combine the filtrate and washings. After cooling, titrate with 0.1 mol/L silver nitrate VS until the color of the precipitate changes from yellow to green (indicator: 1 mL of tetrabromophenolphthalein ethyl ester TS).

Each mL of 0.1 mol/L silver nitrate VS  
= 19.031 mg of  $C_{11}H_{12}I_3NO_2$

**Containers and storage** Containers—Tight containers.

Storage—Light-resistant.

## Iopanoic Acid Tablets

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Iopanoic Acid Tablets contain not less than 95% and not more than 105% of the labeled amount of