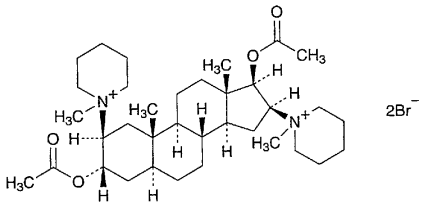
Pancuronium Bromide

臭化パンクロニウム



$C_{35}H_{60}Br_2N_2O_4$: 732.67
1,1′-(3α,17β-Diacetoxy-5α-androstan-2β,16β-diyl)bis(1-methylpiperidinium) dibromide [*15500-66-0*]

Pancuronium Bromide contains not less than 98.0% and not more than 102.0% of $C_{35}H_{60}Br_2N_2O_4$, calculated on the dehydrated basis.

Description Pancuronium Bromide occurs as a white crystalline powder.

It is very soluble in water, and freely soluble in ethanol (95) and in acetic anhydride.

It is hygroscopic.

Identification **(1)** Determine the infrared absorption spectrum of Pancuronium Bromide 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.

(2) A solution of Pancuronium Bromide (1 in 100) responds to the Qualitative Tests (1) for bromide.

Optical rotation $[\alpha]_D^{20}$: +38 – +42° (0.75 g calculated on the dehydrated basis, water, 25 mL, 100 mm).

pH The pH of a solution of Pancuronium Bromide (1 in 100) is between 4.5 and 6.5.

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

(2) Related substances—Dissolve 0.050 g of Pancuronium Bromide in 5 mL of ethanol (95), and use this solution as the sample solution. Pipet 1 mL of this solution, add ethanol (95) to make exactly 100 mL, and use this solution as the standard solution (1). Separately, weigh exactly 5 mg of dacuronium bromide for thin-layer chromatography, add ethanol (95) to make exactly 25 mL, and use this solution as the standard solution (2). Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 2 μL each of the sample solution, the standard solution (1) and the standard solution (2) on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of 2-propanol, acetonitrile and a solution of sodium iodide (1 in 5) (17:2:1) to a distance of about 12 cm, and air-dry the plate. Spray evenly a solution of sodium nitrite in methanol (1 in 100) on the plate, allow to stand for 2 minutes, and spray evenly potassium bismuth iodide TS on the plate: a spot from the sample solution, corresponding to that from the standard solution (2), has no more color than that from the standard solution (2), and the spots other than the principal spot and the above mentioned spot from the sample solution have no more color than the spot from the standard solution (1).

Water Not more than 8.0% (0.3 g, volumetric titration, direct titration).

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

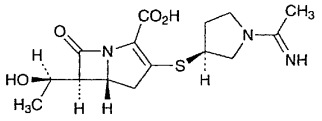
Assay Weigh accurately about 0.2 g of Pancuronium Bromide, dissolve in 50 mL of acetic anhydride by warming, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 36.634 mg of $C_{35}H_{60}Br_2N_2O_4$

Containers and storage Containers—Tight containers.
Storage—Light-resistant.

Panipenem

パニペネム



$C_{15}H_{21}N_3O_4S$: 339.41
(5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-[(3*S*)-1-(1-iminoethyl)pyrrolidin-3-ylsulfanyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid
[*87726-17-8*]

Panipenem contains not less than 900 μg (potency) per mg, calculated on the anhydrous and desolvent basis. The potency of Panipenem is expressed as mass (potency) of panipenem ($C_{15}H_{21}N_3O_4S$).

Description Panipenem occurs as a white to light yellow, crystalline powder or mass.

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

It is hygroscopic.

It deliquesces in the presence of moisture.

Identification **(1)** Dissolve 0.02 g of Panipenem in 2 mL of water, add 1 mL of hydroxylammonium chloride-ethanol TS, allow to stand for 3 minutes, add 1 mL of acidic ammonium iron (III) sulfate TS, and shake: a red-brown color develops.

(2) Determine the absorption spectrum of a solution of Panipenem in 0.02 mol/L 3-(*N*-morpholino)propanesulfonic acid buffer solution, pH 7.0 (1 in 50,000) as directed under the Ultraviolet-visible Spectrophotometry: it exhibits a maximum between 296 nm and 300 nm.

(3) Determine the infrared absorption spectrum of Panipenem as directed in the potassium bromide disk

method under the Infrared Spectrophotometry: it exhibits absorption at the wave numbers of about 1760 cm^{-1}, 1676 cm^{-1}, 1632 cm^{-1}, 1588 cm^{-1}, 1384 cm^{-1} and 1249 cm^{-1}.

Absorbance $E_{1\,cm}^{1\%}$ (298 nm): 280 - 310 (0.05 g calculated on the anhydrous and desolvent basis, 0.02 mol/L 3-(*N*-morpholino)propanesulfonic acid buffer solution, pH 7.0, 2500 mL).

Optical rotation $[\alpha]_D^{20}$: +55 - +65° (0.1 g, calculated on the anhydrous and desolvent basis, 0.1 mol/L 3-(*N*-morpholino)propanesulfonic acid buffer solution, pH 7.0, 10 mL, 100 mm).

pH Dissolve 0.5 g of Panipenem in 10 mL of water: the pH of the solution is between 4.5 and 6.5.

Purity **(1)** Clarity and color of solution—Being specified separately.

(2) Heavy metals—Proceed with 1.0 g of Panipenem according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(3) Residual solvents—Weigh accurately about 0.2 g of Panipenem, transfer to a 20-mL narrow-mouthed cylindrical glass bottle, add exactly 2 mL of the internal standard solution and 2 mL of water to dissolve, seal tightly a rubber stopper with aluminum cap, and use this solution as the sample solution. Separately, pipet 15 mL of ethanol (99.5) and 3 mL of acetone, add water to make exactly 200 mL. Pipet 1 mL and 2 mL of this solution, and add water to them to make exactly 20 mL. Transfer exactly 2 mL each of these solutions to a 20-mL narrow-mouthed cylindrical glass bottle, add exactly 2 mL of the internal standard solution, seal tightly a rubber stopper with aluminum cap, and use these solutions as the standard solution (1) and the standard solution (2). Shake gently in a water bath at a constant room temperature, and allow to stand for 30 minutes. Perform the test with 1 mL of the sample gas in each container as directed under the Gas Chromatography according to the following condition. Calculate the ratios, Q_{Ta} and Q_{Tb}, of the peak area of ethanol and acetone to that of the internal standard from the sample solution, the ratios, Q_{Sa1} and Q_{Sb1}, of the peak area of ethanol and acetone to that of the internal standard from the standard solution (1), and the ratios, Q_{Sa2} and Q_{Sb2}, of the peak area of ethanol and acetone to that of the internal standard from the standard solution (2). Calculate the amount of the ethanol and acetone by the following formula: ethanol is not more than 5.0% and acetone is not more than 1.0%.

$$\text{Amount (\%) of ethanol in Panipenem} = 15 \times 0.79 \times \frac{Q_{Ta} + Q_{Sa2} - 2Q_{Sa1}}{2(Q_{Sa2} - Q_{Sa1})} \times \frac{1}{1000} \times \frac{100}{\text{amount (g) of Panipenem}}$$

$$\text{Amount (\%) of acetone in Panipenem} = 3 \times 0.79 \times \frac{Q_{Tb} + Q_{Sb2} - 2Q_{Sb1}}{2(Q_{Sb2} - Q_{Sb1})} \times \frac{1}{1000} \times \frac{100}{\text{amount (g) of Panipenem}}$$

0.79: Specific gravity (d_{20}^{20}) of ethanol (99.5) and acetone

Internal standard solution—A solution of 1-propanol (1 in 400).

Operating conditions—

Detector: Hydrogen flame-ionization detector

Column: A glass column 1 mm in inside diameter and 40 m in length, coated with porous polymer bead for gas chromatography.

Column temperature: A constant temperature of about 140°C.

Carrier gas: Helium

Flow rate: Adjust the flow rate so that the retention time of 1-propanol is about 6 minutes.

System suitability—

System performance: When the procedure is run with 1 mL of the gas of the standard solution (2) under the above operating conditions, ethanol, acetone and the internal standard are eluted in this order with the resolution between ethanol and acetone being not less than 4.

System repeatability: When the test is repeated 6 times with 1 mL of the gas of the standard solution (2) under the above operating conditions, the relative standard deviation of the ratios of the peak area of ethanol to that of the internal standard is not more than 5.0%.

(4) Related substances—Being specified separately.

Water Weigh accurately about 0.5 g of Panipenem, transfer to a 15-mL narrow-mouthed cylindrical glass bottle, add exactly 2 mL of the internal standard solution to dissolve, seal tightly a rubber stopper with aluminum cap, and use this solution as the sample solution. Separately, weigh accurately 2 g of water, and add the internal standard solution to make exactly 100 mL. Pipet 5 mL and 10 mL of this solution, add the internal standard solution to make exactly 20 mL, and use these solutions as the standard solution (1) and the standard solution (2). Perform the test with 1 μL of the sample solution, the standard solution (1) and the standard solution (2) as directed under the Gas Chromatography according to the following condition, and calculate the ratios, Q_T, Q_{S1} and Q_{S2} of the peak area of water to that of the internal standard. Calculate the amount of water by the following formula: water is not more than 5.0%.

$$\text{Amount of water (\%)} = W \times \frac{Q_T + Q_{S2} - 2Q_{S1}}{2(Q_{S2} - Q_{S1})} \times \frac{1}{100} \times \frac{100}{\text{amount (g) of Panipenem}}$$

W: Amount (g) of weighed water

Internal standard solution—A solution of acetonitrile in methanol (1 in 100).

Operating conditions—

Detector: A thermal conductivity detector

Column: A glass column 3 mm in inside diameter and 2 m in length, packed with porous ethylvinylbenzene-divinylbenzene copolymer for gas chromatography (150 to 180 μm in particle diameter).

Column temperature: A constant temperature of about 125°C.

Carrier gas: Helium

Flow rate: Adjust the flow rate so that the retention time of acetonitrile is about 8 minutes.

System suitability—

System performance: When the procedure is run with 1 μL of the standard solution (2) under the above operating conditions, water, methanol, and the internal standard are eluted in this order with the resolution between water and internal standard being not less than 10.

System repeatability: When the test is repeated 6 times with 1 μL of the standard solution (2) under the above operating conditions, the relative standard deviation of the ratios of the peak area of water to that of the internal standard is not more than 5.0%.

Residue on ignition Being specified separately.

Bacterial endotoxins Less than 0.15 EU/mg (potency).

Assay Weigh accurately an amount of Panipenem and Panipenem Reference Standard, equivalent to about 0.1 g (potency), dissolve separately in 0.02 mol/L 3-(*N*-morpholino)propanesulfonic acid buffer solution, pH 7.0 to make exactly 100 mL. Pipet 5 mL each of these solutions, add exactly 5 mL of the internal solution, add 0.02 mol/L 3-(*N*-morpholino)propanesulfonic acid buffer solution, pH 7.0 to make 20 mL, and use these solutions as the sample solution and the standard solution. Perform the test within 30 minutes after preparation of the solutions with 10 μL of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of panipenem to that of the internal standard.

Amount [μg (potency)] of panipenem ($C_{15}H_{21}N_3O_4S$)
= amount [mg (potency)] of Panipenem Reference Standard $\times \frac{Q_T}{Q_S} \times 1000$

Internal standard solution—A solution of sodium *p*-styrenesulfonate in 0.02 mol/L 3-(*N*-morpholino) propanesulfonic acid buffer solution, pH 7.0 (1 in 1000).

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silicone polymer coated silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: A mixture of 0.02 mol/L 3-(*N*-morpholino)propanesulfonic acid buffer solution, pH 8.0 and acetonitrile (50:1).

Flow rate: Adjust the flow rate so that the retention time of the internal standard is about 12 minutes.

System suitability—

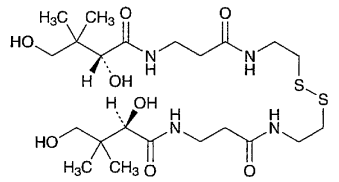
System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, panipenem and the internal standard are eluted in this order with the resolution between these peaks being not less than 3.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratios of the peak area of panipenem to that of the internal standard is not more than 2.0%.

Containers and storage Containers—Tight containers.
Storage—Not exceeding −10°C.

Pantethine

パンテチン



$C_{22}H_{42}N_4O_8S_2$: 554.72
Bis(2-{3-[(2*R*)-2,4-dihydroxy-3,3-dimethylbutanoylamino] propanoylamino}ethyl)disulfide [*16816-67-4*]

Pantethine is an aqueous solution containing 80% of pantethine.

Pantethine contains not less than 98.0% of pantethine ($C_{22}H_{42}N_4O_8S_2$), calculated on the anhydrous basis.

Description Pantethine is a clear, colorless to pale yellow viscous liquid.

It is miscible with water, with methanol and with ethanol (95).

It is decomposed by light.

Identification (1) To 0.7 g of Pantethine add 5 mL of sodium hydroxide TS, shake, and add 1 to 2 drops of copper (II) sulfate TS: a blue-purple color develops.

(2) To 0.7 g of Pantethine add 3 mL of water, shake, add 0.1 g of zinc powder and 2 mL of acetic acid (100), and boil for 2 to 3 minutes. After cooling, add 1 to 2 drops of sodium pentacyanonitrosylferrate (III) TS: a red-purple color develops.

(3) To 1.0 g of Pantethine add 500 mL of water, and shake. To 5 mL of this solution add 3 mL of 1 mol/L hydrochloric acid TS, and heat on a water bath for 30 minutes. After cooling, add 7 mL of a solution of hydroxylammonium chloride in sodium hydroxide TS (3 in 140), and allow to stand for 5 minutes. Add 3 drops of 2,4-dinitrophenol TS, and add 1 mol/L hydrochloric acid TS dropwise until the solution has no color, and then add 1 mL of iron (III) chloride TS: a red-purple color develops.

Optical rotation $[\alpha]_D^{20}$: +15.0 – +18.0° (1 g calculated on the anhydrous basis, water, 25 mL, 100 mm).

Purity (1) Heavy metals—Proceed with 2.0 g of Pantethine according to Method 1, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(2) Arsenic—Prepare the test solution with 2.0 g of Pantethine according to Method 3, and perform the test using Apparatus B (not more than 1 ppm).

(3) Related substances—Dissolve 0.6 g of Pantethine in 10 mL of water, and use this solution as the sample solu-