N^1-{4-[3-(Guanidinobutyl)guanidino]butyl}-bleomycinamide sulfate
[*9041-93-4*, Bleomycin Sulfate]

Bleomycin Sulfate conforms to the requirements of Bleomycin Sulfate in the Requirements for Antibiotic Products of Japan.

Description Bleomycin Sulfate occurs as a white to yellowish white powder.

It is freely soluble in water, very slightly soluble in ethanol (95), and practically insoluble in diethyl ether.

Boric Acid

ホウ酸

H_3BO_3: 61.83

Boric Acid, when dried, contains not less than 99.5% of H_3BO_3.

Description Boric Acid occurs as colorless or white crystals or crystalline powder. It is odorless, and has a slight, characteristic taste.

It is freely soluble in warm water, in hot ethanol (95) and in glycerin, soluble in water and in ethanol (95), and practically insoluble in diethyl ether.

The pH of a solution of Boric Acid (1 in 20) is between 3.5 and 4.1.

Identification A solution of Boric acid (1 in 20) responds to the Qualitative Tests for borate.

Purity **(1)** Clarity and color of solution—Dissolve 1.0 g of Boric acid in 25 mL of water or in 10 mL of hot ethanol (95): the solution is clear and colorless.

(2) Heavy metals—Proceed with 2.0 g of Boric Acid 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).

(3) Arsenic—Prepare the test solution with 0.40 g of Boric Acid according to Method 1, and perform the test using Apparatus B (not more than 5 ppm).

Loss on drying Not more than 0.5% (2 g, silica gel, 5 hours).

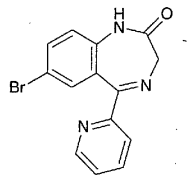
Assay Weigh accurately about 1.5 g of Boric Acid, previously dried, add 15 g of D-sorbitol and 50 mL of water, and dissolve by warming. After cooling, titrate with 1 mol/L sodium hydroxide VS (indicator: 2 drops of phenolphthalein TS).

Each mL of 1 mol/L sodium hydroxide VS
= 61.83 mg of H_3BO_3

Containers and storage Containers—Well-closed containers.

Bromazepam

ブロマゼパム



$C_{14}H_{10}BrN_3O$: 316.15
7-Bromo-1,3-dihydro-5-(pyridin-2-yl)-2*H*-1,4-benzodiazepin-2-one [*1812-30-2*]

Bromazepam, when dried, contains not less than 99.0% of $C_{14}H_{10}BrN_3O$.

Description Bromazepam occurs as white to light yellowish white crystals or crystalline powder. It is odorless.

It is freely soluble in *N,N*-dimethylformamide and in acetic acid (100), sparingly soluble in chloroform, slightly soluble in methanol and in ethanol (99.5), very slightly soluble in diethyl ether, and practically insoluble in water.

It dissolves in dilute hydrochloric acid.

Melting point: about 245°C (with decomposition).

Identification **(1)** Dissolve 0.01 g of Bromazepam in 5 mL of dilute hydrochloric acid, heat in a water bath for 10 minutes, and cool: the solution responds to the Qualitative Tests for primary aromatic amines.

(2) To 10 mL of a solution of Bromazepam in chloroform (1 in 10,000) add 5 mL of diluted iron (II) sulfate TS (1 in 8), and shake: a red-purple color develops in the water layer.

(3) Determine the absorption spectrum of a solution of Bromazepam in ethanol (99.5) (1 in 200,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) To 0.3 g of Bromazepam in a porcelain crucible add 0.5 g of anhydrous sodium carbonate, stir well, and carbonize by ignition. After cooling, to the residue add 15 mL of hot water, heat on a water bath for 5 minutes, and filter. Render the filtrate slightly acidic with dilute hydrochloric acid: the solution responds to the Qualitative Tests for bromide.

Purity **(1)** Chloride—To 1.0 g of Bromazepam add 50 mL of water, allow to stand for 1 hour with occasional shaking, and filter. To 25 mL of the filtrate add 6 mL of dilute nitric acid and water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution as follows: to 0.25 mL of 0.01 mol/L hydrochloric acid VS add 6 mL of dilute nitric acid and water to make 50 mL (not more than 0.018%).

(2) Heavy metals—Proceed with 1.0 g of Bromazepam in a platinum crucible 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) Arsenic—Dissolve 1.0 g of Bromazepam in 15.0 mL of *N,N*-dimethylformamide. Perform the test with this solu-

tion using Apparatus B (not more than 2 ppm).

(4) Related substances—Dissolve 0.050 g of Bromazepam in 5 mL of a mixture of chloroform and methanol (4:1), and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add a mixture of chloroform and methanol (4:1) to make exactly 50 mL. Pipet 5 mL of this solution, add a mixture of chloroform and methanol (4:1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 20 μL each of the sample solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, ammonia solution (28) and ethanol (99.5) (38:1:1) to a distance of about 12 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): the spots other than the principal spot from the sample solution and the spot of the starting point are not more than 2, and not more intense than the spot from the standard solution.

Loss on drying Not more than 0.20% (1 g, 105°C, 4 hours).

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

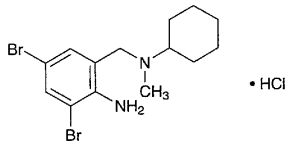
Assay Weigh accurately about 0.4 g of Bromazepam, previously dried, dissolve in 80 mL of acetic acid (100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 31.616 mg of $C_{14}H_{10}BrN_3O$

Containers and storage Containers—Well-closed containers.

Bromhexine Hydrochloride

塩酸ブロムヘキシン



$C_{14}H_{20}Br_2N_2.HCl$: 412.59
N-(2-Amino-3,5-dibromophenylmethyl)-*N*-cyclohexyl-*N*-methylamine monohydrochloride [*611-75-6*]

Bromhexine Hydrochloride, when dried, contains not less than 98.5% of $C_{14}H_{20}Br_2N_2.HCl$.

Description Bromhexine Hydrochloride occurs as white crystals or crystalline powder.

It is freely soluble in formic acid, sparingly soluble in methanol, and slightly soluble in water and in ethanol (95).

The pH of its saturated solution is between 3.0 and 5.0.

Melting point: about 239°C (with decomposition).

Identification (1) Dissolve 3 mg of Bromhexine Hydrochloride in 0.01 mol/L hydrochloric acid TS to make 100 mL. Determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

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

(3) Add 20 mL of water to 1 g of Bromhexine Hydrochloride. After thorough shaking, add 3 mL of sodium hydroxide TS, and extract with four 20-mL portions of diethyl ether. Neutralize the water layer with dilute nitric acid: the solution responds to the Qualitative Tests (2) for chloride.

Purity (1) Heavy metals—Proceed with 2.0 g of Bromhexine Hydrochloride according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(2) Related substances—Conduct this procedure without exposure to daylight, using light-resistant vessels. Dissolve 0.050 g of Bromhexine Hydrochloride in 10 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add the mobile phase to make exactly 20 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 5 μL 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 by the automatic integration method: each peak area other than bromhexine is not larger than the peak area of bromhexine of the standard solution.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 245 nm).

Column: A stainless steel column about 5 mm in inside diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

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

Mobile phase: Dissolve 1.0 g of potassium dihydrogen phosphate in 900 mL of water, adjust the pH to 7.0 with 0.5 mol/L sodium hydroxide TS, and add water to make 1000 mL. To 200 mL of this solution add 800 mL of acetonitrile.

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

Selection of column: To 0.05 g of bamethane sulfate add 0.5 mL of the sample solution, and add the mobile phase to make 10 mL. Proceed with 5 μL of this solution under the above operating conditions, and calculate the resolution. Use a column giving elution of bamethane and bromhexine in this order with the resolution between these peaks being not less than 7.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of bromhexine from 5 μL of the standard solution is between 5 mm and 15 mm.

Time span of measurement: About 2 times as long as the retention time of bromhexine after the solvent peak.

Loss on drying Not more than 0.5% (1 g, 105°C, 4 hours).