

principal spot from the sample solution are not more intense than the spot from the standard solution.

**Water** Not more than 1.5% (2 g, direct titration).

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

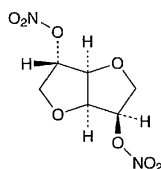
**Assay** Weigh accurately about 10 g of Isosorbide, calculated on the anhydrous basis, and dissolve in water to make exactly 100 mL. Determine the optical rotation,  $\alpha_D$ , of this solution at  $20 \pm 1^\circ\text{C}$  in a 100-mm cell.

$$\text{Amount (g) of } \text{C}_6\text{H}_{10}\text{O}_4 = \alpha_D \times 2.1978$$

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

## Isosorbide Dinitrate

硝酸イソソルビド



$\text{C}_6\text{H}_8\text{N}_2\text{O}_8$ : 236.14

1,4:3,6-Dianhydro-D-glucitol dinitrate [87-33-2]

Isosorbide Dinitrate contains not less than 95.0% of  $\text{C}_6\text{H}_8\text{N}_2\text{O}_8$ , calculated on the anhydrous basis.

**Description** Isosorbide Dinitrate occurs as white crystals or crystalline powder. It is odorless or has a faint odor like that of nitric acid.

It is very soluble in *N,N*-dimethylformamide and in acetone, freely soluble in chloroform and in toluene, soluble in methanol, in ethanol (95) and in diethyl ether, and practically insoluble in water.

It explodes if heated quickly or subjected to percussion.

**Identification (1)** Dissolve 0.01 g of Isosorbide Dinitrate in 1 mL of water, and dissolve by adding 2 mL of sulfuric acid cautiously. After cooling, superimpose 3 mL of iron (II) sulfate TS, and allow to stand for 5 to 10 minutes: a brown ring is produced at the zone of contact.

**(2)** Dissolve 0.1 g of Isosorbide Dinitrate in 6 mL of diluted sulfuric acid (1 in 2) by heating in a water bath. After cooling, add 1 mL of a solution of potassium permanganate (1 in 30), stir well, and heat in a water bath until the color of potassium permanganate disappears. Add 10 mL of 2,4-dinitro-phenylhydrazine TS, and heat in a water bath: an orange precipitate is produced.

**Optical rotation**  $[\alpha]_D^{20}$ :  $+134 - +139^\circ$  (1 g, calculated on the anhydrous basis, ethanol (95), 100 mL, 100 mm).

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

**(2)** Sulfate—Dissolve 1.5 g of Isosorbide Dinitrate in 15 mL of *N,N*-dimethylformamide, add 60 mL of water, cool, and filter. Wash the filter paper with three 20-mL portions of water, combine the washings with the filtrate, and add

water to make 150 mL. To 40 mL of this solution add 1 mL of dilute hydrochloric acid and water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid VS (not more than 0.048%).

**(3)** Nitrate—Dissolve 0.05 g of Isosorbide Dinitrate in 30 mL of toluene, and extract with three 20-mL portions of water. Combine the aqueous layers, and wash with two 20-mL portions of toluene. To the aqueous layer add water to make 100 mL, and use this solution as the sample solution. Pipet 5.0 mL of Standard Nitric Acid Solution and 25 mL of the sample solution in each Nessler tube, and add water to make 50 mL, respectively. To each of them add 0.06 g of Griss-Romijn's nitric acid reagent, stir well, allow to stand for 30 minutes, and observe from the side of the Nessler tube: the sample solution has no more color than the standard solution.

**(4)** Heavy metals—Dissolve 1.0 g of Isosorbide Dinitrate in 30 mL of acetone, and add 2 mL of dilute acetic acid and water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution as follows: to 2.0 mL of Standard Lead Solution add 30 mL of acetone, 2 mL of dilute acetic acid and water to make 50 mL (not more than 20 ppm).

**Water** Not more than 1.5% (0.3 g, direct titration).

**Assay** Weigh accurately about 0.1 g of Isosorbide Dinitrate in a Kjeldahl flask as described under the Nitrogen Determination, dissolve in 10 mL of methanol, add 3 g of Devarda's alloy and 50 mL of water, and connect the flask with the distillation apparatus as described under the Nitrogen Determination. Measure exactly 25 mL of 0.05 mol/L sulfuric acid VS in an absorption flask, add 5 drops of bromocresol green-methyl red TS, and immerse the lower end of the condenser tube in it. Add 15 mL of a solution of sodium hydroxide (1 in 2) through the funnel, cautiously rinse the funnel with 20 mL of water, immediately close the clamp attached to the rubber tubing, then begin the distillation with steam gradually, and continue the distillation until the distillate measures 100 mL. Remove the absorption flask, rinse the end of the condenser tube with a small quantity of water, and titrate the distillate and the rinsings with 0.1 mol/L sodium hydroxide VS until the color of the solution changes from red through light red-purple to light blue-green. Perform a blank determination.

$$\begin{aligned} \text{Each mL of 0.05 mol/L sulfuric acid VS} \\ = 11.807 \text{ mg of } \text{C}_6\text{H}_8\text{N}_2\text{O}_8 \end{aligned}$$

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

Storage—Light-resistant, and in a cold place.

## Isosorbide Dinitrate Tablets

硝酸イソソルビド錠

Isosorbide Dinitrate Tablets contain not less than 93% and not more than 107% of the labeled amount of isosorbide dinitrate ( $\text{C}_6\text{H}_8\text{N}_2\text{O}_8$ : 236.14).

**Method of preparation** Prepare as directed under Tablets, with Isosorbide Dinitrate.

**Identification** Weigh a quantity of powdered Isosorbide Dinitrate Tablets, equivalent to 0.1 g of Isosorbide Dinitrate according to the labeled amount, add 50 mL of diethyl ether, shake well, and filter. Measure 5 mL of the filtrate, evaporate to dryness cautiously, add 1 mL of water to the residue, and dissolve by adding 2 mL of sulfuric acid cautiously. After cooling, superimpose 3 mL of iron (II) sulfate TS, and allow to stand for 5 to 10 minutes: a brown ring is produced at the zone of contact.

**Purity** Free nitrate ion—Weigh accurately a quantity of powdered Isosorbide Dinitrate Tablets, equivalent to 0.05 g of Isosorbide Dinitrate according to the labeled amount, transfer to a separator, add 30 mL of toluene, shake thoroughly, extract with three 20-mL portions of water, and proceed as directed in Purity (3) under Isosorbide Dinitrate.

**Disintegration test** Isosorbide Dinitrate Tablets meet the requirements of the Disintegration Test. For sublingual tablets, the time limit of the test is 2 minutes, and omit the use of the disk.

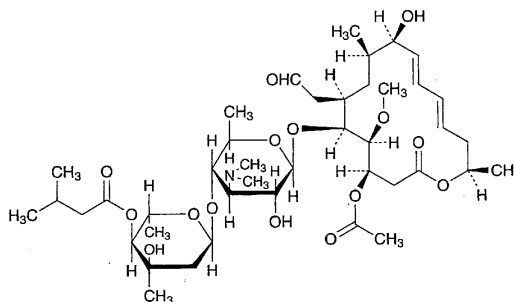
**Assay** Weigh accurately and powder not less than 20 Isosorbide Dinitrate Tablets. Weigh accurately a portion of the powder, equivalent to about 5 mg of isosorbide dinitrate ( $C_6H_8N_2O_8$ ), add exactly 50 mL of acetic acid (100), shake for 15 minutes, filter, and use this filtrate as the sample solution. Separately, weigh accurately about 0.09 g of potassium nitrate, previously dried at 105°C for 4 hours, dissolve in 5 mL of water, and add acetic acid (100) to make exactly 100 mL. Measure exactly 10 mL of this solution, add acetic acid (100) to make exactly 100 mL, and use this solution as the standard solution. Measure exactly 2 mL each of the sample solution and the standard solution, add exactly 2.5 mL of salicylic acid TS to each, shake well, allow to stand for 15 minutes, and add 10 mL of water. Make them alkaline with about 12 mL of a solution of sodium hydroxide (2 in 5) while cooling in an ice bath, and add water to make exactly 50 mL. Perform the test with these solutions as directed under the Ultraviolet-visible Spectrophotometry, using a solution, prepared with 2 mL of glacial acetic in the same manner, as the blank. Determine the absorbances,  $A_T$  and  $A_S$ , of the subsequent solutions of the sample solution and the standard solution at 412 nm, respectively.

$$\begin{aligned} \text{Amount (mg) of isosorbide dinitrate (C}_6\text{H}_8\text{N}_2\text{O}_8\text{)} \\ &= \text{amount (mg) of potassium nitrate} \\ &\times \frac{A_T}{A_S} \times \frac{1}{20} \times 1.1679 \end{aligned}$$

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

## Josamycin

ジョサマイシン



$C_{42}H_{69}NO_{15}$ : 827.99

(3*R*,4*R*,5*S*,6*R*,8*R*,9*R*,10*E*,12*E*,15*R*)-3-Acetoxy-5-[*O*-2,6-dideoxy-4-*O*-(3-methylbutanoyl)-3-*C*-methyl- $\alpha$ -*L*-ribohexopyranosyl-(1 $\rightarrow$ 4)-3,6-dideoxy-3-dimethylamino- $\beta$ -*D*-glucopyranosyloxy]-6-formylmethyl-9-hydroxy-4-methoxy-8-methylhexadeca-10,12-dien-15-olide [16846-24-5]

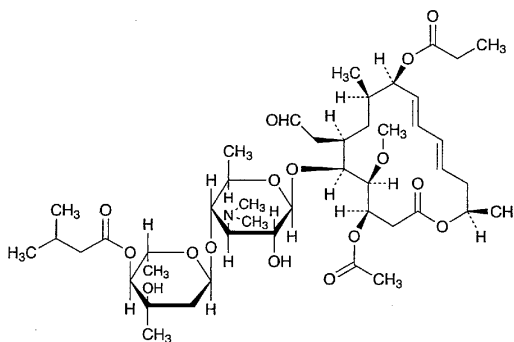
Josamycin conforms to the requirements of Josamycin in the Requirements for Antibiotic Products of Japan.

**Description** Josamycin occurs as a white to yellowish white powder. It has a bitter taste.

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

## Josamycin Propionate

プロピオン酸ジョサマイシン



$C_{45}H_{73}NO_{16}$ : 884.06

(3*R*,4*R*,5*S*,6*R*,8*R*,9*R*,10*E*,12*E*,15*R*)-3-Acetoxy-5-[*O*-2,6-dideoxy-4-*O*-(3-methylbutanoyl)-3-*C*-methyl- $\alpha$ -*L*-ribohexopyranosyl-(1 $\rightarrow$ 4)-3,6-dideoxy-3-dimethylamino- $\beta$ -*D*-glucopyranosyloxy]-6-formylmethyl-4-methoxy-8-methyl-9-propionyloxyhexadeca-10,12-dien-15-olide [16846-24-5, Josamycin]

Josamycin Propionate conforms to the requirements of Josamycin Propionate in Requirements for Antibiotic Products of Japan.