Mobile phase: Dissolve 0.32 g of tetra *n*-butylammonium bromide, 3.22 g of disodium hydrogenphosphate 12-water and 6.94 g of potassium dihydrogenphosphate in 1000 mL of water. To 840 mL of this solution add 1160 mL of methanol.

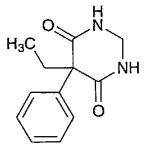
Flow rate: Adjust the flow rate so that the retention time of prednisolone succinate is about 15 minutes.

Selection of column: Proceed with 10 μL of the standard solution under the above operating conditions, and calculate the resolution. Use a column giving elution of prednisolone succinate and the internal standard in this order with the resolution between these peaks being not less than 6.

Containers and storage Containers—Hermetic containers.

Primidone

プリミドン



$C_{12}H_{14}N_2O_2$: 218.25

5-Ethyldihydro-5-phenylpyrimidine-4,6(1*H*,5*H*)-dione

[*125-33-7*]

Primidone, when dried, contains not less than 98.5% of $C_{12}H_{14}N_2O_2$.

Description Primidone occurs as a white, crystalline powder or granules. It is odorless and has a slightly bitter taste.

It is soluble in *N,N*-dimethylformamide, sparingly soluble in pyridine, slightly soluble in ethanol (95), very slightly soluble in water, and practically insoluble in diethyl ether.

Identification **(1)** Heat 0.5 g of Primidone with 5 mL of diluted sulfuric acid (1 in 2): the odor of formaldehyde is perceptible.

(2) Mix 0.2 g of Primidone with 0.2 g of anhydrous sodium carbonate, and heat: the gas evolved changes moistened red litmus paper to blue.

Melting point 279 - 284°C

Purity **(1)** Clarity and color of solution—Dissolve 0.10 g of Primidone in 10 mL of *N,N*-dimethylformamide: the solution is clear and colorless.

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

(3) 2-Ethyl-2-phenylmalonediamide—Dissolve 0.10 g of Primidone in 2 mL of pyridine, add exactly 2 mL of the internal standard solution, then add 1 mL of bis-trimethyl silyl acetamide, shake well, and heat at 100°C for 5 minutes. Cool, add pyridine to make 10 mL, and use this solution as the sample solution. Separately, dissolve 0.050 g of 2-ethyl-2-phenylmalonediamide in pyridine to make exactly 100 mL. Pipet 2 mL of this solution, add exactly 2 mL of the internal standard solution, proceed in the same manner as Primidone, and use this solution as the standard solution. Perform the test with 2 μL of the sample solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of 2-ethyl-2-phenylmalonediamide to that of the internal standard: Q_T is not more than Q_S.

Internal standard solution—A solution of stearylalcohol in pyridine (1 in 2000).

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A glass column about 3 mm in inside diameter and about 1.5 m in length, packed with siliceous earth for gas chromatography (125 to 150 μm in particle diameter) coated with 50% phenyl-methyl silicon polymer for gas chromatography at the ratio of 3%.

Column temperature: A constant temperature of about 195°C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of stearylalcohol is 8 to 9 minutes.

Selection of column: Proceed with 2 μL of the standard solution under the above operating condition, and calculate the resolution. Use a column giving elution of 2-ethyl-2-phenylmalonediamide and the internal standard in this order with the resolution between these peaks being not less than 3.

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

Residue on ignition Not more than 0.20% (1 g).

Assay Weigh accurately about 0.02 g each of Primidone and Primidone Reference Standard, previously dried, dissolve each in 20 mL of ethanol (95) by warming, and after cooling, add ethanol (95) to make exactly 25 mL, and use these solutions as the sample solution and the standard solution, respectively. Determine the absorbance, A_1, of the sample solution and the standard solution at the wavelength of maximum absorption at about 257 nm, and the absorbances, A_2 and A_3, at the wavelength of minimum absorption at about 254 nm and at about 261 nm, as directed under the Ultraviolet-visible Spectrophotometry, using ethanol (95) as the blank.

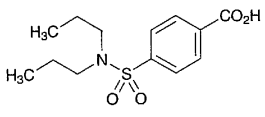
$$\text{Amount (mg) of } C_{12}H_{14}N_2O_2 = \text{amount (mg) of Primidone Reference Standard} \times \frac{(2A_1 - A_2 - A_3)_T}{(2A_1 - A_2 - A_3)_S},$$

where, $(2A_1 - A_2 - A_3)_T$ is the value from the sample solution, and $(2A_1 - A_2 - A_3)_S$ is from the standard solution.

Containers and storage Containers—Tight containers.

Probenecid

プロベネシド



$C_{13}H_{19}NO_4S$: 285.36

4-(Dipropylaminosulfonyl)benzoic acid [*57-66-9*]

Probenecid, when dried, contains not less than 98.0% of $C_{13}H_{19}NO_4S$.

Description Probenecid occurs as white crystals or crystalline powder. It is odorless, and has a slightly bitter taste, followed by unpleasant bitter.

Probenecid is sparingly soluble in ethanol (95), slightly soluble in diethyl ether, and practically insoluble in water.

It dissolves in sodium hydroxide TS and in ammonia TS.

Melting point: 198 - 200°C

Identification (1) Heat Probenecid strongly: the odor of sulfur dioxide is perceptible.

(2) Determine the absorption spectrum of a solution of Probenecid in ethanol (95) (1 in 50,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Probenecid Reference Standard prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

Purity (1) Acid—To 2.0 g of Probenecid add 100 mL of water, heat on a water bath with occasional shaking for 30 minutes, cool, and filter. To the filtrate add 1 drop of phenolphthalein TS and 0.50 mL of 0.1 mol/L sodium hydroxide VS: a red color develops.

(2) Chloride—To 1.0 g of Probenecid add 100 mL of water and 1 mL of nitric acid, and heat on a water bath with occasional shaking for 30 minutes. After cooling, add, if necessary, water to make 100 mL, and filter. Perform the test using 50 mL of the filtrate as the test solution. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid VS (not more than 0.021%).

(3) Sulfate—To 1.0 g of Probenecid add 100 mL of water and 1 mL of hydrochloric acid, and heat on a water bath with occasional shaking for 30 minutes. After cooling, add, if necessary, water to make 100 mL, and filter. Perform the test using 50 mL of the filtrate as the test solution. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid VS (not more than 0.038%).

(4) Heavy metals—Proceed with 2.0 g of Probenecid 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).

(5) Arsenic—Prepare the test solution with 1.0 g of Probenecid 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, 4 hours).

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

Assay Weigh accurately about 0.5 g of Probenecid, previously dried, and dissolve in 50 mL of neutralized ethanol. Titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS).

Each mL of 0.1 mol/L sodium hydroxide VS
= 28.536 mg of $C_{13}H_{19}NO_4S$

Containers and storage Containers—Well-closed containers.

Probenecid Tablets

プロベネシド錠

Probenecid Tablets contain not less than 95% and not more than 105% of the labeled amount of probenecid ($C_{13}H_{19}NO_4S$: 285.36).

Method of preparation Prepare as directed under Tablets, with Probenecid.

Identification (1) Weigh a quantity of powdered Probenecid Tablets, equivalent to 0.5 g of Probenecid according to the labeled amount, add 50 mL of ethanol (95) and 1 mL of 1 mol/L hydrochloric acid TS, shake, and filter. Evaporate the filtrate on a water bath to about 20 mL. After cooling, collect produced crystals, recrystallize with 50 mL of dilute ethanol, and dry at 105°C for 4 hours: it melts between 198°C and 200°C. With the crystals so obtained, proceed as directed in the Identification (1) under Probenecid.

(2) Determine the absorption spectrum of a solution of the dried crystals obtained in (1) in ethanol (95) (1 in 50,000) as directed under the Ultraviolet-visible Spectrophotometry: it exhibits maxima between 224 nm and 226 nm and between 247 nm and 249 nm, and a minimum between 234 nm and 236 nm.

Dissolution test Perform the test with 1 tablet of Probenecid Tablets at 50 revolutions per minute according to Method 2 under the Dissolution Test, using 900 mL of diluted phosphate buffer solution, pH 6.8, (1 in 2) as the test solution. Take 30 mL or more of the dissolved solution 30 minutes after start of the test, and filter through a membrane filter with pore size of not more than 0.8 μm. Discard the first 10 mL of the filtrate, pipet the subsequent V mL, add diluted phosphate buffer solution, pH 6.8, (1 in 2) to make exactly V' mL so that each mL contains about 14 μg of probenecid ($C_{13}H_{19}NO_4S$) according to the labeled amount, and use this solution as the sample solution. Separately, weigh accurately about 0.07 g of Probenecid Reference Standard, previously dried at 105°C for 4 hours, and dissolve in diluted phosphate buffer solution, pH 6.8, (1 in 2) to make exactly 100 mL. Pipet 1 mL of this solution, add diluted phosphate buffer solution, pH 6.8, (1 in 2) to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the sample solution and the standard solution at 244 nm as directed under the Ultraviolet-visible Spectrophotometry.

The dissolution rate of Probenecid Tablets in 30 minutes is not less than 80%.

Dissolution rate (%) with respect to the labeled amount of probenecid ($C_{13}H_{19}NO_4S$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 18$$

W_S: Amount (mg) of Probenecid Reference Standard.

C: Labeled amount (mg) of probenecid ($C_{13}H_{19}NO_4S$) in 1 tablet.

Assay Weigh accurately, and powder not less than 20 Probenecid Tablets. Weigh accurately a portion of the powder, equivalent to about 0.15 g of probenecid ($C_{13}H_{19}NO_4S$), add 200 mL of ethanol (95) and 5 mL of 1 mol/L