other than the area of the haloxazolam from the sample solution is not larger than the peak area of the haloxazolam from the standard solution.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 250 nm).

Column: A stainless steel column about 4 mm in inside diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Column temperature: Room temperature.

Mobile phase: Dissolve 6.2 g of boric acid and 7.5 g of potassium chloride in 900 mL of water, adjust the pH with triethylamine to 8.5, and add water to make 1000 mL. To 3 volumes of this solution add 2 volumes of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of haloxazolam is about 10 minutes.

Selection of column: Dissolve 0.01 g each of Haloxazolam and cloxazolam in 200 mL of acetonitrile. Proceed with 10 μL of this solution under the above operating conditions, and calculate the resolution. Use a column giving elution of Haloxazolam and cloxazolam in this order with the resolution between these peaks being not less than 1.5.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of haloxazolam obtained from 10 μL of the standard solution is between 5 mm and 15 mm.

Time span of measurement: About 3 times as long as the retention time of haloxazolam after the solvent peak.

Loss on drying Not more than 0.5% (1 g, 105°C, 3 hours).

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

Assay Weigh accurately about 0.5 g of Haloxazolam, previously dried, dissolve in 50 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
= 37.721 mg of $C_{17}H_{14}BrFN_2O_2$

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

Heparin Sodium

ヘパリンナトリウム

Heparin Sodium is obtained from the livers, the lungs and the intestinal mucosa of healthy edible animals, and prolongs the clotting time of blood. Heparin Sodium obtained from the livers and the lungs contains not less than 110 Heparin Units per mg, and that obtained from the intestinal mucosa contains not less than 130 Heparin Units per mg.

Heparin Sodium, calculated on the dried basis, contains not less than 90% and not more than 110% of the labeled Units.

Label the name of the organ used as the starting material.

Description Heparin Sodium occurs as a white to grayish brown powder or grains. It is odorless.

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

It is hygroscopic.

pH The pH of a solution of 1.0 g of Heparin Sodium in 100 mL of water is between 6.0 and 8.0.

Purity **(1)** Clarity and color of solution—Dissolve 0.5 g of Heparin Sodium in 20 mL of water: the solution is clear and colorless to light yellow.

(2) Barium—Dissolve 0.03 g of Heparin Sodium in 3.0 mL of water, and use this solution as the sample solution. To 1.0 mL of the sample solution add 3 drops of dilute sulfuric acid, and allow to stand for 10 minutes: no turbidity is produced.

(3) Total nitrogen—Weigh accurately about 0.1 g of Heparin Sodium, previously dried at 60°C for 3 hours under reduced pressure, and perform the test as directed under the Nitrogen Determination: the amount of nitrogen (N: 14.01) is not more than 3.0%.

(4) Protein—To 1.0 mL of the sample solution obtained in (2) add 5 drops of a solution of trichloroacetic acid (1 in 5): neither a precipitate nor turbidity is produced.

Loss on drying Not more than 10% (0.02 g, in vacuum, 60°C, 3 hours).

Residue on ignition Not more than 40% (after drying, 0.02 g).

Pyrogen Dissolve Heparin Sodium in isotonic sodium chloride solution so as to contain 1000 Units per mL according to the labeled Units. Inject into rabbits 2 mL of this solution per kg: it meets the requirements of the Pyrogen Test.

Assay (i) Standard solution: Dissolve Heparin Sodium Reference Standard in water so as to contain exactly 2.00 and 1.60 Units per ml, and use them as the high-dose standard solution (S_H) and the low-dose standard solution (S_L), respectively.

(ii) Sample solution: Weigh accurately appropriate amounts of Heparin Sodium according to the labeled Units, dissolve in water so as to contain exactly 2.00 and 1.60 Units per ml, and use them as the high-dose sample solution (T_H) and the low-dose sample solution (T_L), respectively.

(iii) Sulfated whole blood: Place 250 mL of fresh bovine blood in a wide-mouthed stoppered polyethylene bottle containing 50 mL of a solution of sodium sulfate decahydrate (9 in 50), and store at 1 to 4°C. Remove any clotted substance before use.

(iv) Acetone-dried cattle brain: Mince fresh cattle brains after removing blood vessels, connective tissues and other similar matters from them, and place in 10 volumes of acetone to dehydrate. Place 30 g of the dehydrated minced brains in a mortar. Grind with each 75 mL of acetone and dehydrate completely. Dry at 37°C for 2 hours to remove acetone completely.

(v) Thrombokinase extract: To 1.5 g of acetone-dried cattle brain add 60 mL of water, extract at 50°C for 10 to 15 minutes, and centrifuge for 2 minutes at 1500 revolutions per minute. To the supernatant add cresol to make 0.3% as a preservative, and store between 1°C and 4°C. The potency of this solution will be maintained for a few days.

(vi) Procedure: In 4 clean 13 × 150 mm glass-stoppered test tubes, place 1 mL each of S_H, S_L, T_H and T_L separately. To each tube add 0.20 mL of the thromobokinase extract: the amount of the thrombokinase extract should be controlled so that the longest coagulation time is 9 to 12 minutes. Then, to each tube add 1 mL of the sulfated whole blood, stopper each tube, mix by inverting the tubes gently, and observe each tube by gentle tilting at 15-second intervals. The coagulation time is the time required for the formation of a solid clot on the bottom of the tube which does not come down when inverting the tube. If a tube has been inverted before the coagulation is completed, stop the test, and try the test again. Repeat the complete test more than four times.

(vii) Method of calculation: Designate the logarithms of the coagulation time for each dose groups of S_H, S_L, T_H and T_L as y_1, y_2, y_3 and y_4, respectively. Sum up y_1, y_2, y_3 and y_4 for each test and designate them as Y_1, Y_2, Y_3 and Y_4, respectively.

Units per mg of Heparin Sodium
= antilog M × (units per mL of the high-dose standard solution)
$\times \frac{b}{a}$

$$M = \frac{IY_a}{Y_b}$$

$$I = \log\frac{S_H}{S_L} = \log\frac{T_H}{T_L}$$

$$Y_a = -Y_1 - Y_2 + Y_3 + Y_4$$

$$Y_b = Y_1 - Y_2 + Y_3 - Y_4$$

a: Mass (mg) of Heparin Sodium sample.
b: Total volume (mL) of the high-dose sample solution prepared by dissolving Heparin Sodium in water.

Compute L (P = 0.95) by using the following equation: L is not more than 0.15. If L exceeds 0.15, increase the number of the tests until L reaches 0.15 or less.

$$L = 2\sqrt{(C-1)(CM^2 + I^2)}$$

$$C = \frac{Y_b^2}{Y_b^2 - 4fs^2t^2}$$

f: The number of the runs.

$$s^2 = \frac{\Sigma y^2 - \frac{Y}{f} - \frac{Y'}{4} + \frac{Y''}{4f}}{n}$$

Σy^2: The sum of the squares of each y_1, y_2, y_3 and y_4 in each test.
$Y = Y_1^2 + Y_2^2 + Y_3^2 + Y_4^2$
Y': The sum of the squares of the sum of y_1, y_2, y_3 and y_4 in each test, for the whole run.
$Y'' = (Y_1 + Y_2 + Y_3 + Y_4)^2$
$n = 3(f-1)$
t^2: Value shown in the table in the Assay under Insulin Injection against n for which s^2 is calculated.

Containers and storage Containers—Tight containers.

Heparin Sodium Injection

ヘパリンナトリウム注射液

Heparin Sodium Injection is an aqueous solution for injection. It contains not less than 90% and not more than 110% of the labeled heparin Units.

Label the name of organ used as the starting material of Heparin Sodium supplied for preparing Heparin Sodium Injection.

Method of preparation Dissolve Heparin Sodium in Isotonic Sodium Chloride Solution and prepare as directed under Injections.

Description Heparin Sodium Injection is a clear, colorless to light yellow liquid.

pH 5.5 – 8.0

Purity **(1)** Barium—Measure exactly a portion of Heparin Sodium Injection, equivalent to 3000 Units of Heparin Sodium according to the labeled Unit. Add water to make 3.0 mL and use this solution as the sample solution. To 1.0 mL of the sample solution add 3 drops of dilute sulfuric acid, and allow to stand for 10 minutes: no turbidity is produced.

(2) Protein—Proceed as directed in the Purity (4) under Heparin Sodium.

Bacterial endotoxins Less than 0.0030 EU/unit.

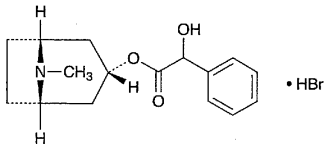
Assay Proceed as directed in the Assay under Heparin Sodium. However, the sample solutions indicated in (ii) are as follows.

Sample solution: Measure exactly adequate portions of Heparin Sodium Injection according to the labeled Units, dilute them with water so as to obtain two solutions containing exactly 2.00 and 1.60 Units per ml, and use them as high-dose (T_H) and low-dose (T_L) sample solutions, respectively.

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

Homatropine Hydrobromide

臭化水素酸ホマトロピン



$C_{16}H_{21}NO_3.HBr$: 356.25
(1*R*,3*r*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl [(*RS*)-2-hydroxy-2-phenyl]acetate monohydrobromide [*51-56-9*]

Homatropine Hydrobromide contains not less than 99.0% of $C_{16}H_{21}NO_3.HBr$, calculated on the dried basis.

Description Homatropine Hydrobromide occurs as white