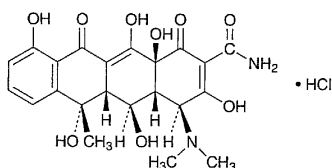


Oxytetracycline Hydrochloride

塩酸オキシテトラサイクリン



$C_{22}H_{24}N_2O_9 \cdot HCl$: 496.89

(4*S*,4*aR*,5*S*,5*aR*,6*S*,12*aS*)-4-Dimethylamino-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3,5,6,10,12,12*a*-hexahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide monohydrochloride [2058-46-0]

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

Description Oxytetracycline Hydrochloride occurs as yellow crystals or crystalline powder. It has a bitter taste.

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

Oxytocin Injection

オキシトシン注射液

Oxytocin Injection is an aqueous solution for injection, and contains synthetic oxytocin, or the oxytocic principle, oxytocin, obtained from the posterior lobe of the pituitary of healthy cattle, pigs and other mammals, from which most of the pressor principle, vasopressin, has been removed.

Oxytocin Injection contains not less than 85% and not more than 120% of the labeled Oxytocin Units.

Method of preparation Prepare as directed under Injections, with oxytocin obtained from the posterior lobe of the pituitary or synthetic oxytocin.

Description Oxytocin Injection is a colorless, clear liquid. It is odorless or has a slight, characteristic odor.

pH 2.5 – 4.5

Purity Pressor principle—Proceed with Oxytocin Injection as follows: not more than 0.5 vasopressin Units for each labeled 10 oxytocin Units. To prepare the sample solution according to (iv), assuming that the vasopressin Units in Oxytocin Injection amount to 1/20 of the labeled oxytocin Units.

(i) Test animals: Use health male rats weighing between 200 g and 300 g.

(ii) Standard stock solution: Weigh accurately 0.02 to 0.05 g of Posterior Pituitary Reference Standard, place in a conical flask, and add exactly 0.5 mL of diluted acetic acid (100) (1 in 400) per 1.0 Unit. Insert a small funnel into the neck of the flask, and heat the mixture with shaking gently in a water bath for 5 minutes. Cool the flask quickly to ordi-

nary temperature, and filter: 1 mL of the filtrate is equivalent to 2.0 Unites. Place this filtrate in hard glass ampules, seal and sterilize at 100°C for 30 minutes. Store in a cold place, and do not freeze. Use within 6 months after preparation.

(iii) Standard solution: Dilute the standard stock solution with isotonic sodium chloride solution so that 0.2 mL of the obtained solution causes blood pressure increases of between 35 mmHg and 60 mmHg in test animals when injected according to (vi), and designate this solution as the high-dose standard solution (S_H). Then dilute this solution with isotonic sodium chloride solution 1.5 to 2.0 times by volume, and designate it as the low-dose standard solution (S_L).

(iv) Sample solution: Dilute an accurately measured volume of Oxytocin Injection with isotonic sodium chloride solution so that the obtained solution contains the same concentration in Units as the high-dose standard solution based on the labeled Units, and designate it as the high-dose sample solution (T_H). Then dilute this solution with isotonic sodium chloride solution 1.5 to 2.0 times by volume and designate it as the low-dose sample solution (T_L). Make the concentration ratio of S_H to S_L equal to the ratio of T_H to T_L . When the sensitivity of an animal is changed, adjust the concentration of S_H and T_H before the next set of assay is started. However, keep the same ratio of S_H to S_L and T_H to T_L as in the primary set.

(v) Dose of injection: Although 0.2 mL of each solution is usually injected, the dose of injection can be determined based from preliminary tests or experiences. Inject the same volume throughout a set of tests.

(vi) Procedure: Inject subcutaneously 0.7 mL of a solution of ethyl carbamate (1 in 4) per 100 g of body mass to anesthetize the test animals and cannulate the trachea. Under artificial respiration (about 60 strokes per minute), remove a part of the second cervical vertebra, cut off the spinal cord and destroy the brain through the foramen magnum. Insert a cannula filled with isotonic sodium chloride solution into a femoral vein. Through this cannula, inject a solution prepared by dissolving 200 heparin Units of heparin sodium in 0.1 mL of isotonic sodium chloride solution, and then immediately inject 0.3 mL of isotonic sodium chloride solution. Insert a cannula into a carotid artery, and connect the cannula to a manometer for blood pressure measurement with a vinyl tube. The cannula and the vinyl tube has previously been filled with isotonic sodium chloride solution. Inject the standard and the sample solutions at regular intervals of 10 to 15 minutes into the femoral vein through the cannula followed by 0.3 mL of the isotonic solution when the blood pressure increase caused by each solution returns to the original level. Measure the height of blood pressure increase within 1 mmHg on the kymogram. Maintain a constant temperature between 20°C and 25°C during the assay. In advance, make four pairs with S_H , S_L , T_H , T_L as follows. Randomize the order of injection for pairs, but keep the order of injection within pairs as indicated.

Pair 1: S_H , T_L Pair 2: S_L , T_H Pair 3: T_H , S_L Pair 4: T_L , S_H

Carry out this assay using the same animals throughout a set of four pairs of observations. Perform this assay with two sets. If necessary, however, the different animals may be used for both sets of tests.

(vii) Calculation: Subtract increases of blood pressure

caused by the low dose from those caused by the high dose in the Pair 1, 2, 3 and 4 of each set, and obtain the responses y_1, y_2, y_3 and y_4 , respectively. Sum up y_1 , for each set to obtain Y_1 , and obtain Y_2, Y_3 and Y_4 in the same way, and calculate the pressure unit using the formula shown in (vii) Calculation in the Assay.

Assay (i) **Test animal:** Select a healthy young adult male chicken weighing between 1.5 kg and 2.5 kg. If severe tachyphylaxis, as shown by a rapidly decreasing response to several successive injection, occurs, do not use that chicken.

(ii) **Standard stock solution:** Weigh accurately 0.02 to 0.05 g of Posterior Pituitary Reference Standard, place in a conical flask, and add exactly 0.5 mL of diluted acetic acid (100) (1 in 400) per 1.0 Unit. Insert a small funnel into the neck of the flask. Heat the mixture, with shaking gently in a water bath for 5 minutes. Cool the flask quickly to ordinary temperature, and filter: 1 mL of the filtrate is equivalent to 2.0 Units. Place this filtrate in hard glass ampules, seal and sterilize at 100°C for 30 minutes. Store in a cold place, and do not freeze. Use within 6 months from the date of preparation.

(iii) **Standard solution:** Dilute the standard stock solution with isotonic sodium chloride solution so that 0.15 to 0.5 mL of the resulting diluted solution causes a consistent but evanescent decrease in the blood pressure of the test animals by 30 to 40 mm of mercury when given according to procedure (vi), and designate this solution as the high-dose standard solution (S_H). Dilute it to 1.5 to 2.0 times with isotonic sodium chloride solution, and designate this solution as the low-dose standard solution (S_L).

(iv) **Sample solution:** Measure exactly a portion of Oxytocin Injection according to the labeled Units, dilute with isotonic sodium chloride solution, so that the resulting test solution contains the same Units in the same volumes as the high-dose standard solution, and designate this solution as a high-dose sample solution (T_H). Dilute this solution to 1.5 to 2.0 times with isotonic sodium chloride solution, and designate this solution as a low-dose sample solution (T_L). The concentration ratio of S_H to S_L and that of T_H to T_L should be equal. If the responses were decreased, the concentrations of S_H and T_H should be adjusted before the next set of tests, but the ratio of S_H to S_L or T_H to T_L is the same as in the primary one.

(v) **Dose for injection:** Select the doses of injection according to the results of preliminary tests or the experience of the experimenter. Inject a fixed identical volume, usually 0.15 to 0.5 mL, throughout the whole run. The volumes of injection should be the same throughout a set of tests.

(vi) **Procedure:** Anesthetize the test animal deeply enough to prevent voluntary muscular movements, by injecting into the gastronegus 2 mL per kg of body mass of a solution of phenobarbital sodium (1 in 10) prepared before use. If necessary, inject a further amount of a solution of phenobarbital sodium (1 in 10). Remove the ramal arteries by careful dissection, expose an ischiatic artery and insert a cannula. Connect this artery cannula to a manometer for blood pressure measurement with a vinyl tube. The cannula and the vinyl tube are previously filled with a solution of trisodium citrate dihydrate (17 in 200). Inject the standard and the sample solutions at regular intervals of 3 to 10 minutes into the femoral or brachial vein when the

decreased blood pressure which is caused by the standard or the sample solution has returned almost to the original level. Read the blood pressure decreases to within 1 mmHg on a kymogram. Keep a temperature between 20°C and 25°C during the assay. In advance, make four pairs from S_H, S_L, T_H and T_L as follows. Randomize the order of injection for pairs, but maintain the indicated sequence of doses within each pair.

Pair 1: S_H, T_L Pair 2: S_L, T_H Pair 3: T_H, S_L Pair 4: T_L, S_H

Proceed with this assay using the same animal throughout a set of four pairs of observations. Carry out this assay usually with two sets.

(vii) **Calculation:** Subtract the decreases of the blood pressure at the low dose from the high dose of each pair to obtain the responses y_1, y_2, y_3 and y_4 , respectively. Sum up y_1, y_2, y_3 and y_4 on each set to obtain Y_1, Y_2, Y_3 and Y_4 .

Units per mL of Oxytocin Injection

$$= \text{antilog } M \times \left(\frac{\text{units per mL of the high-dose standard solution}}{\text{dose standard solution}} \right) \times \frac{b}{a}$$

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

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

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

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

a : Volume (mL) of Oxytocin Injection sampled.

b : Total volume (mL) of the high-dose sample solution prepared by diluting with isotonic sodium chloride solution.

Compute L ($P=0.95$) by the following equation, and confirm L to be 0.15 or less. If L exceeds 0.15, repeat the test, improving the conditions of the assay or, increasing the number of sets, until L reaches to 0.15 or less.

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

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

f : Number of sets

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

Σy^2 : The sum of the squares of each y_1, y_2, y_3 and y_4

$$Y = Y_1^2 + Y_2^2 + Y_3^2 + Y_4^2$$

Y' : The sum of the squares of the sum of y_1, y_2, y_3 and y_4 in each set

$$n = 3(f-1)$$

t^2 : Value shown in the table of the Assay under Insulin Injection against n for which s^2 is calculated.

Containers and storage Containers—Hermetic containers.

Storage—In a cold place, and avoid freezing.

Expiration date 36 months after preparation.