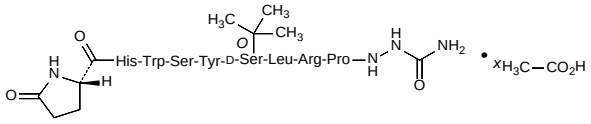
Goserelin Acetate

ゴセレリン酢酸塩



$C_{59}H_{84}N_{18}O_{14}.xC_2H_4O_2$

2-(5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*O*-*tert*-butyl-D-seryl-L-leucyl-L-arginyl-L-prolyl)hydrazine-1-carboxamide acetate

[*145781-92-6*]

Goserelin Acetate contains not less than 94.5% and not more than 103.0% of goserelin ($C_{59}H_{84}N_{18}O_{14}$: 1269.41), calculated on the anhydrous and residual acetic acid-free basis.

Description Goserelin Acetate occurs as a white powder.

It is freely soluble in acetic acid (100), soluble in water, and slightly soluble in ethanol (95).

It is hygroscopic.

Identification **(1)** Adjust the pHs of solutions of Goserelin Acetate and Goserelin Acetate RS in deuterated water for nuclear magnetic resonance spectroscopy (1 in 10) to 4.0 with deuterated acetic acid for nuclear magnetic resonance spectroscopy, and use these solutions as the sample solution and the standard solution. Determine the ^{13}C spectra of these solution as directed under Nuclear Magnetic Resonance Spectroscopy *<2.21>* with ^{1}H-decoupling, and compare the spectra: both spectra exhibit signals with similar integrated intensities at the same chemical shifts.

Furthermore, determine the ^{13}C spectra of these solutions under the following conditions, measure the integrated intensities of the signals around 23.5 ppm, 26.0 ppm, 26.3 ppm, 41.8 ppm, 55.7 ppm, 62.2 ppm, 62.5 ppm, 116.7 ppm, 118.4 ppm, and 162.2 ppm corresponding to leucine, proline, pyroglutamic acid, arginine, tryptophan, *tert*-butylserine, tyrosine, histidine, and azoglycine in the sample solution and standard solution, and define the ratio of the integrated intensity of each signal in the sample solution to that of the individual signal in the standard solution as the amino acid ratio: the amino acid ratios of leucine, proline, pyroglutamic acid, arginine, tryptophan, tert-butylserine, tyrosine, and histidine are 0.9 to 1.1, and that of azoglycine is 0.8 to 1.2.

Operating conditions—

Apparatus: Not less than 100 MHz.

Measuring spectrum range: 0 – 200 ppm.

Temperature: A constant temperature of about 25°C

(2) Perform the test with 10 μL each of the sample solution and the standard solution obtained in the Assay as directed under Liquid Chromatography *<2.01>* according to the conditions described in the Assay: the retention times of the principal peaks obtained from the sample solution and standard solution are the same.

Optical rotation *<2.49>* $[\alpha]_D^{20}$: −52 – −56° (20 mg calculated on the anhydrous and residual acetic acid-free basis, water, 10 mL, 100 mm).

Acetic acid Weigh accurately about 15 mg of Goserelin Acetate calculated on the anhydrous basis, add water to make exactly 5 mL, and use this solution as the sample solution. Separately, dissolve potassium acetate (CH_3COOK: 98.15) in water to make solutions so that each mL contains 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg and 0.5 mg, and use these solutions as the standard solutions (1), (2), (3), (4) and (5). Perform the test with exactly 20 μL each of the sample solution and standard solutions (1), (2), (3), (4) and (5) as directed under Liquid Chromatography *<2.01>* according to the following conditions. Calculate the concentration of acetic acid (mg/mL) in the sample solution using the calibration curve obtained with the standard solutions, and determine the content of acetic acid in Goserelin Acetate by the following equation: 4.5 – 10.0%.

Content of acetic acid (%)
$= 1/M_T \times$ volume of sample solution (mL) $\times 5 \times 100$

M_T: Amount (mg) of Goserelin Acetate taken, calculated on the anhydrous basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: A mixture of water, methanol, phosphoric acid and ammonium water (25) (968:20:7:5).

Flow rate: 1.5 mL per minute.

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution (1) under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of acetic acid are not less than 3500 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution (1) under the above operating conditions, the relative standard deviation of the peak area of acetic acid is not more than 3.0%.

Purity Related substances—Use the sample solution in the Assay as the sample solution. Pipet 1 mL of the sample

solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine each peak area in each solution by the automatic integration method: the peak area of the related substance E, having the relative retention time of about 0.89 to goserelin, obtained from the sample solution is not larger than the peak area of goserelin from the standard solution, each peak area of other related substances from the sample solution is not larger than 1/2 times the peak area of goserelin from the standard solution. Furthermore, the total area of the peaks other than goserelin from the sample solution is not larger than 2.5 times the peak area of goserelin from the standard solution.

Operating conditions—

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 2 times as long as the retention time of goserelin.

System suitability—

System performance: Proceed as directed in the system suitability in the Assay.

Test for required detectability: Pipet 1 mL of the standard solution obtained in the Assay, add water to make exactly 200 mL, and use this solution as the solution for system suitability test. Pipet 10 mL of the solution for system suitability test, and add water to make exactly 100 mL. Confirm that the peak area of goserelin obtained with 10 μL of this solution is equivalent to 7 to 13% of that with 10 μL of the solution for system suitability test.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of goserelin is not more than 3%.

Water <2.48> Not more than 10.0% (20 mg, coulometric titration).

Assay Weigh accurately about 25 mg of Goserelin Acetate and Goserelin Acetate RS (previously determine the water <2.48> and acetic acid in the same manner as Goserelin), dissolve each in water to make exactly 25 mL, respectively, and use these solutions as the sample solution and the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S, of goserelin in each solution.

Amount (mg) of goserelin ($C_{59}H_{84}N_{18}O_{14}$)
$= M_S \times A_T / A_S$

M_S: Amount (mg) of Goserelin Acetate RS taken, calculated on the anhydrous and residual acetic acid-free basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3.5 μm in particle diameter).

Column temperature: A constant temperature of about 53°C.

Mobile phase: A mixture of water, acetonitrile for liquid chromatography and trifluoroacetic acid (1600:400:1).

Flow rate: Adjust so that the retention time of goserelin is between 40 and 50 minutes.

System suitability—

System performance: Mix equal volumes of the diluted sample solution (1 in 10) and a solution of Goserelin Acetate Related Substance for System Suitability RS (1 in 10000). When the procedure is run with 10 μL of this solution under the above operating conditions, [4-D-serine]goserelin and goserelin are eluted in this order with the resolution between these peaks being not less than 7, and the symmetry factor of the peak of goserelin is between 0.8 and 2.5.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of goserelin is not more than 2.0%.

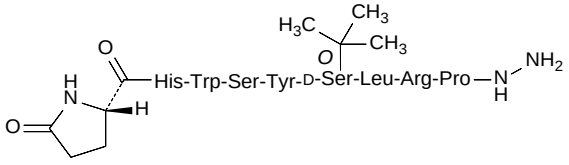
Containers and storage Containers—Tight containers.

Storage—Light-resistant, at a temperature between 2°C and 8°C.

Others

Related substance E:

5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*O*-*tert*-butyl-D-seryl-L-leucyl-L-arginyl-L-prolinohydrazide



Add the following to 9.01 Reference Standards (1):

Goserelin Acetate RS

Goserelin Acetate Related Substance for System Suitability RS

Add the following to 9.41 Reagents, Test Solutions:

Deuterated acetic acid for nuclear magnetic resonance spectroscopy CD_3CO_2D Prepared for nuclear magnetic resonance spectroscopy.