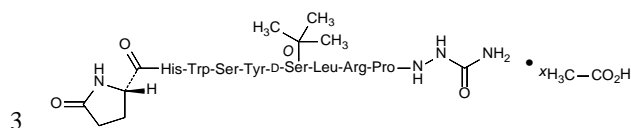


1 Goserelin Acetate

2 ゴセレリン酢酸塩



4 $C_{59}H_{84}N_{18}O_{14} \cdot xC_2H_4O_2$

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

8 [145781-92-6]

9

10 Goserelin Acetate contains not less than 94.5% and
11 not more than 103.0% of goserelin ($C_{59}H_{84}N_{18}O_{14}$:
12 1269.41), calculated on the anhydrous and residual acetic
13 acid-free basis.

14 **Description** Goserelin Acetate occurs as a white powder.

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

17 It is hygroscopic.

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

28 Furthermore, determine the ^{13}C spectra of these solutions
29 under the following conditions, measure the integrated intensities
30 of the signals around 23.5 ppm, 26.0 ppm, 26.3 ppm,
31 41.8 ppm, 55.7 ppm, 62.2 ppm, 62.5 ppm, 116.7 ppm, 118.4
32 ppm, and 162.2 ppm corresponding to leucine, proline, pyroglutamic
33 acid, arginine, tryptophan, *tert*-butylserine, tyrosine, histidine,
34 and azoglycine in the sample solution and standard solution, and
35 define the ratio of the integrated intensity of each signal in the
36 sample solution to that of the individual signal in the standard
37 solution as the amino acid ratio: the amino acid ratios of leucine,
38 proline, pyroglutamic acid, arginine, tryptophan, *tert*-butylserine,
39 tyrosine, and histidine are 0.9 to 1.1, and that of azoglycine is
40 0.8 to 1.2.

41 **Operating conditions**—

42 Apparatus: Not less than 100 MHz.

43 Measuring spectrum range: 0 – 200 ppm.

44 Temperature: A constant temperature of about 25°C

45 **(2)** Perform the test with 10 μL each of the sample solution
46 and the standard solution obtained in the Assay as

47 directed under Liquid Chromatography <2.01> according to
48 the conditions described in the Assay: the retention times of
49 the principal peaks obtained from the sample solution and
50 standard solution are the same.

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

54 **Acetic acid** Weigh accurately about 15 mg of Goserelin
55 Acetate calculated on the anhydrous basis, add water to make
56 exactly 5 mL, and use this solution as the sample solution.
57 Separately, dissolve potassium acetate (CH_3COOK : 98.15) in
58 water to make solutions so that each mL contains 0.1 mg, 0.2
59 mg, 0.3 mg, 0.4 mg and 0.5 mg, and use these solutions as
60 the standard solutions (1), (2), (3), (4) and (5). Perform the
61 test with exactly 20 μL each of the sample solution and standard
62 solutions (1), (2), (3), (4) and (5) as directed under Liquid
63 Chromatography <2.01> according to the following conditions.
64 Calculate the concentration of acetic acid (mg/mL) in the sample
65 solution using the calibration curve obtained with the standard
66 solutions, and determine the content of acetic acid in Goserelin
67 Acetate by the following equation: 4.5 –
68 10.0%.

69 Content of acetic acid (%)

70 $= 1/M_T \times \text{volume of sample solution (mL)} \times 5 \times 100$

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

73 **Operating conditions**—

74 Detector: An ultraviolet absorption photometer (wavelength:
75 210 nm).

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

79 Column temperature: A constant temperature of about
80 25°C.

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

83 Flow rate: 1.5 mL per minute.

84 **System suitability**—

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

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

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

96 solution, add water to make exactly 100 mL, and use this so-
 97 lution as the standard solution. Perform the test with exactly
 98 10 μL each of the sample solution and standard solution as
 99 directed under Liquid Chromatography <2.01> according to
 100 the following conditions, and determine each peak area in
 101 each solution by the automatic integration method: the peak
 102 area of the related substance E, having the relative retention
 103 time of about 0.89 to goserelin, obtained from the sample so-
 104 lution is not larger than the peak area of goserelin from the
 105 standard solution, each peak area of other related substances
 106 from the sample solution is not larger than 1/2 times the peak
 107 area of goserelin from the standard solution. Furthermore, the
 108 total area of the peaks other than goserelin from the sample
 109 solution is not larger than 2.5 times the peak area of goserelin
 110 from the standard solution.

111 *Operating conditions—*

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

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

117 *System suitability—*

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

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

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

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

134 **Assay** Weigh accurately about 25 mg of Goserelin Acetate
 135 and Goserelin Acetate RS (previously determine the water
 136 <2.48> and acetic acid in the same manner as Goserelin), dis-
 137 solve each in water to make exactly 25 mL, respectively, and
 138 use these solutions as the sample solution and the standard
 139 solution. Perform the test with exactly 10 μL each of the sam-
 140 ple solution and standard solution as directed under Liquid
 141 Chromatography <2.01> according to the following condi-
 142 tions, and determine the peak areas, A_T and A_S , of goserelin
 143 in each solution.

144 Amount (mg) of goserelin ($\text{C}_{59}\text{H}_{84}\text{N}_{18}\text{O}_{14}$)
 145 $=M_S \times A_T/A_S$

146 M_S : Amount (mg) of Goserelin Acetate RS taken, calcu-
 147 lated on the anhydrous and residual acetic acid-free
 148 basis

149 *Operating conditions—*

150 Detector: An ultraviolet absorption photometer (wave-
 151 length: 220 nm).

152 Column: A stainless steel column 4.6 mm in inside diam-
 153 eter and 15 cm in length, packed with octadecylsilanized sil-
 154 ica gel for liquid chromatography (3.5 μm in particle diam-
 155 eter).

156 Column temperature: A constant temperature of about
 157 53°C.

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

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

162 *System suitability—*

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

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

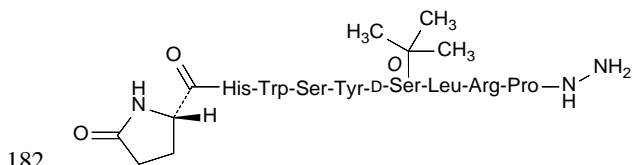
175 **Containers and storage** Containers—Tight containers.

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

178 **Others**

179 Related substance E:

180 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*O*-tert-
 181 butyl-D-seryl-L-leucyl-L-arginyl-L-prolinohydrazide



183 **Add the following to 9.01 Reference**
 184 **Standards (1):**

185 Goserelin Acetate RS

186 Goserelin Acetate Related Substance for System Suitabil-
 187 ity RS

188 *Add the following to 9.41 Reagents, Test*
189 *Solutions:*

190 **Deuterated acetic acid for nuclear magnetic resonance**
191 **spectroscopy** $\text{CD}_3\text{CO}_2\text{D}$ Prepared for nuclear magnetic
192 resonance spectroscopy.
193