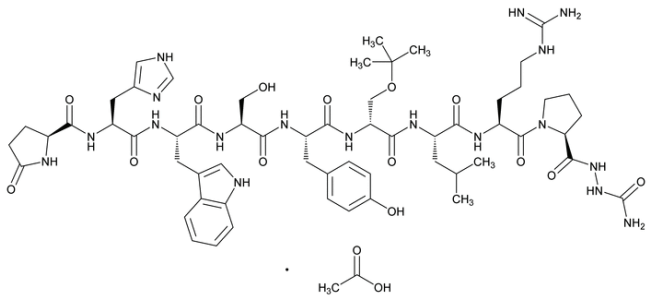
Goserelin Acetate



$C_{59}H_{84}N_{18}O_{14} \cdot xC_2H_4O_2$ 1269.43 (as free base)

Luteinizing hormone-releasing factor (pig), 6-[*O*-(1,1-Dimethylethyl)-D-serine]-10-deglycinamide-, 2-(aminocarbonyl)hydrazide, acetate (salt);
1-(5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*O*-*tert*-butyl-D-seryl-L-leucyl-L-arginyl-L-prolyl)semicarbazide (goserelin free base);
Free base: [65807-02-5].
Acetate salt: [145781-92-6].

DEFINITION

Goserelin Acetate is a synthetic nonapeptide analog of the hypothalmic decapeptide, gonadorelin. It is obtained by chemical synthesis and is available as an acetate salt. It contains NLT 94.5% and NMT 103.0% of goserelin ($C_{59}H_{84}N_{18}O_{14}$), calculated on the anhydrous and acetic acid-free basis.

IDENTIFICATION

• **A.** The retention time of the goserelin peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

• **Procedure**

Mobile phase: Prepare a filtered and degassed mixture of water, acetonitrile, and trifluoroacetic acid (1600:400:1).

Standard solution: 1 mg/mL of USP Goserelin Acetate RS in water

Diluted standard solution: Transfer 1 mL of the *Standard solution* to a 10-mL volumetric flask, and dilute with water to volume.

System suitability solution 1: ▲Prepare a solution of 0.1 mg/mL USP Goserelin Related Compound A RS in water, and mix with an equal volume of *Diluted standard solution*.▲ (IRA 1-May-2020)

System suitability solution 2: ▲Prepare USP Goserelin System Suitability Mixture RS as indicated on the label.▲ (IRA 1-May-2020)

Sample solution: 1 mg/mL of Goserelin Acetate in water

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 50°–55°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Samples: *Standard solution*, *System suitability solution 1*, and *System suitability solution 2*

[Note—For *System suitability solution 1*, the retention time for the goserelin peak is between 40 and 50 min; see *Table 1* for the relative retention times. Two minor peaks are visible prior to the elution of the principal peak, *System suitability solution 2*.]

Suitability requirements

Resolution: NLT 7.0 between the goserelin and goserelin related compound A (4-D-Ser-goserelin) peaks, *System suitability solution 1*

Relative standard deviation: NMT 2.0% for the goserelin peak from replicate injections, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of goserelin ($C_{59}H_{84}N_{18}O_{14}$) in the portion of Goserelin Acetate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
C_U = concentration of the *Sample solution* (mg/mL)

Acceptance criteria: 94.5%–103.0% on the anhydrous, acetic acid-free basis

OTHER COMPONENTS

Delete the following:

▲• **Limit of Acetic Acid**

Mobile phase: Transfer 49.04 g of sulfuric acid to a 1000-mL volumetric flask, dilute with water to volume, and mix. Accurately transfer 20 mL of this solution to a 2000-mL volumetric flask, dilute with water to volume, mix, filter, and degas.

Standard stock solution: Transfer 2.0 mL of glacial acetic acid to a 500-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Standard solution: Transfer 5.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Sample solution: Dissolve about 20 mg of Goserelin Acetate, accurately weighed, in 2–3 mL of *Mobile phase*. Connect a 1-mL cartridge containing packing L44 to a 1-mL cartridge containing packing L2, which is then attached to a suitable vacuum apparatus. With the vacuum applied, wash the cartridge combination with 2 mL of methanol followed by 15 mL of *Mobile phase*, and discard the washings. Quantitatively apply the solution containing the sample to the cartridge combination, and wash through the cartridge system with several small volumes of *Mobile phase*. Collect the solution and washings in a 10-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*).

[Note—Condition the column for about 24 h until a stable baseline is obtained.]

Mode: LC

Detector: UV 206 nm

Column: 7.8-mm × 30-cm; packing L17

Column temperature: 65°

Flow rate: 0.8 mL/min

Injection volume: 100 µL

System suitability:

Sample: *Standard solution*

[Note—The retention time of the acetic acid peak is about 11 min.]

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 3.1%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of acetic acid in the portion of Goserelin Acetate taken by the formula:

$$\text{Result} = (r_U/r_S) \times (1/W) \times (1.049/5)$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
W = sample weight of Goserelin Acetate taken to prepare the *Sample solution* (g) and corrected (for the purposes of the calculation) to eliminate the water content, which is determined immediately prior to the test
1.049 = weight of glacial acetic acid (g/mL)

Acceptance criteria: 4.5%–15.0%▲ (IRA 1-May-2020)

Add the following:

▲• **Acetic Acid in Peptides** ⟨503⟩**:** 4.5%–15.0%▲ (IRA 1-May-2020)

IMPURITIES

Change to read:

• **Organic Impurities: Related Compounds**
Mobile phase, Standard solution, Diluted standard solution, System suitability solution 1, System suitability solution 2, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
Diluted sample solution: Transfer 1 mL of the *Sample solution* into a 100-mL volumetric flask, and dilute with water to volume.
System suitability
Samples: *System suitability solution 1* and *System suitability solution 2*
[Note—For *System suitability solution 1*, the retention time for the goserelin peak is between 40 and 50 min; see *Table 1* for the relative retention times. For *System suitability solution 2*, two peaks, corresponding to decarbamoylgoserelin and 2-D-His-goserelin and eluting prior to the principal peak, are visible.]
Resolution: NLT 7.0, *System suitability solution 1*
Column efficiency: NLT 2000 theoretical plates, ▲*System suitability solution 1*▲ (IRA 1-May-2020)
Tailing factor: NMT 2.0, ▲*System suitability solution 1*▲ (IRA 1-May-2020)
Relative standard deviation: NMT 2.0%, *System suitability solution 2*

Table 1

Name	Relative Retention Time
4-D-Ser-goserelin	0.67
Decarbamoylgoserelin	0.89
5-D-Tyr-goserelin	0.92
2-D-His-goserelin	0.94
Goserelinare	1.0

Analysis
Samples: *Sample solution* and *Diluted sample solution*
Calculate the percentage of goserelin-related impurities in the portion of Goserelin Acetate taken:

$$\text{Result} = r_I/r_U$$

r_I = peak response for any individual impurity in the *Sample solution*
r_U = peak response of the main goserelin peak in the *Diluted sample solution*

Acceptance criteria
Decarbamoylgoserelin: NMT 1.0%
Any other impurity: NMT 0.5%
Total impurities: NMT 2.5%

SPECIFIC TESTS

Change to read:

• ▲**Amino Acid Content**
(See *Nuclear Magnetic Resonance Spectroscopy* ⟨761⟩.)▲ (IRA 1-May-2020)
[Note—Concentrations of goserelin in the *Standard solution* and the *Sample solution* must be the same (within 5% of each other) but can be adjusted based on the quality of the carbon-13 spectra obtained. The spectra must be acquired under the same conditions for both the *Standard solution* and the *Sample solution*. The spectra obtained are of sufficient quality to allow quantification of the integrals of the resonances specified in this test. Integrals and spectra of the *Standard solution* and the *Sample solution* can be repeated and averaged.]
Standard solution: Dissolve USP Goserelin Acetate RS in deuterium oxide to obtain a solution having a known concentration of about 10% (w/v), and adjust with deuterated acetic acid-d4 to a pH of 4.
Sample solution: Prepare a 10% (w/v) solution of Goserelin Acetate in deuterium oxide, and adjust with deuterated acetic acid-d4 to a pH of 4.
Analysis
Samples: *Standard solution* and *Sample solution*
Obtain a carbon-13, proton-decoupled nuclear magnetic resonance (NMR) spectrum of both the *Standard solution* and the *Sample solution*. The spectra from the solutions are qualitatively similar, and all the resonances from the spectrum of the *Standard solution* are present in the spectrum of the *Sample solution* and have the same chemical shift values (±0.1 ppm for goserelin, ±0.5 ppm for acetate). Identify any other resonances in the spectrum of the *Sample solution*. Integrate the resonances at the approximate parts per million corresponding to each amino acid in *Table 2*.

Table 2

Amino Acids	Resonances (ppm)
Azo-glycine	162.2
Histidine	118.4
Tyrosine	116.7
tert-Butyl serine	▲62.2▲ (IRA 1-May-2020)
Serine	▲62.5▲ (IRA 1-May-2020)
Tryptophan	55.7
Arginine	41.8
Pyroglutamic acid	26.3
Proline	26.0
Leucine	23.5

Calculate the ratio of each of the amino acids from the integrals of the *Standard solution* and the *Sample solution*:

$$\text{Result} = r_U/r_S$$

r_U = integral of the resonance of a designated amino acid from the *Sample solution*
r_S = integral of the resonance of a designated amino acid from the *Standard solution*

Acceptance criteria: 0.9–1.1 for histidine, tyrosine, *tert*-butyl serine, serine, tryptophan, arginine, pyroglutamic acid, proline, and leucine ; 0.8–1.2 for azo-glycine

- **Optical Rotation** ⟨781S⟩**,** *Procedures, Specific Rotation*
  Sample solution: 2 mg/mL, in water, calculated on the anhydrous and acetic acid-free basis
  Acceptance criteria: Between –52° and –56°

Change to read:

- **Bacterial Endotoxins Test** ⟨85⟩**:** ▲The level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Goserelin Acetate is used can be met. Where the label states Goserelin Acetate must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Goserelin Acetate is used can be met.▲ (IRA 1-May-2020)
- **Water Determination** ⟨921⟩**,** *Method I***:** NMT 10.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers, and store in a refrigerator.
- **USP Reference Standards** ⟨11⟩
  USP Goserelin Acetate RS
  USP Goserelin Related Compound A RS
  USP Goserelin System Suitability Mixture RS