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Goserelin Implants

DEFINITION

Goserelin Implants are extended-release formulations of a sterile dispersion of Goserelin Acetate in a matrix of D,L-lactic and glycolic acids copolymer (PLGA) that is subcutaneously injected. The content of the PLGA and other ingredients is process-specific, and their identity and properties are determined by validated methods. The quality of Goserelin Acetate meets the compendial standard. Goserelin Implants contain NLT 90.0% and NMT 110.0% of the labeled amount of goserelin ($C_{59}H_{84}N_{18}O_{14}$).

IDENTIFICATION

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

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in *Product-Related Substances and Impurities, Procedure 1*.

ASSAY

• **Procedure**

Buffer: 0.1 M sodium perchlorate solution, pH 2.1. [Note—This solution can be prepared as follows. Weigh 167.5 g of 60% (w/v) perchloric acid into a 1-L volumetric flask, then cool the flask on an ice bath. Add 1 M sodium hydroxide to volume. Transfer 100 mL of this 1 M sodium perchlorate solution to a 1-L volumetric flask and add water to volume. Adjust with 20% (w/v) sodium hydroxide to a pH of 2.1.]

Mobile phase: Acetonitrile and *Buffer* (92:8)

Diluent: Acetonitrile and water (85:15)

System suitability solution: 2.0 mg/mL each of USP Goserelin Acetate RS and USP Goserelin Related Compound A RS in *Diluent*

Standard solution: 2.0 mg/mL of USP Goserelin Acetate RS in *Diluent*

Sample solution: Nominally 2.0 mg/mL of goserelin in *Diluent* prepared by adding 10 Implants to a suitable volumetric flask. Add *Diluent* to about 70% of the total volume, and sonicate to dissolve the sample. Cool to room temperature, and dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 7.8-mm × 30-cm; 5-µm packing L33

Flow rate: 1.0 mL/min

Injection volume: 5 µL

Run time: 90 min

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 4.0 between the main goserelin and goserelin related compound A peaks, *System suitability solution*

Tailing factor: NMT 1.5 for the goserelin peak, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

r_U = peak response of goserelin from the *Sample solution*

r_S = peak response of goserelin from the *Standard solution*

C_S = concentration of USP Goserelin Acetate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of goserelin in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **Dissolution ⟨711⟩**

For 3.6-mg Implants

Medium: pH 7.4 phosphate/citrate buffer prepared as follows. Dissolve 25.8 g/L of anhydrous disodium hydrogen phosphate, 1.92 g/L of citric acid, and 0.2 g/L of sodium azide in water. Adjust with anhydrous disodium hydrogen phosphate or citric acid to a pH of 7.4. Pass through a sterile filter of NMT 0.2-µm pore size into a sterile container; 50 mL

Apparatus: 120-mL flat-bottomed, borosilicate glass jar with a tight plastic cap. Incubate at 39 ± 0.5°. [Note—Suitable procedures should be carried out to remove/minimize microbiological contamination on the glassware immediately before the test, e.g., rinse with methanol and dry at 90° for 2 h.]

Times: 168, 336, 408, 504, and 672 h

Sample solutions: Place 5 Implants in each jar, and add 50 mL of *Medium* at ambient temperature to each jar. Place the jars in the incubator. At the times specified, remove the jars from the incubator and allow to cool for 1 h. Swirl gently to mix, and withdraw 5 mL of aliquot. Replace the aliquot withdrawn with the same volume of *Medium* at ambient temperature into the jar, and return to the incubator 2 h after removal. Dilute each sample with *Medium* (1:1).

For 10.8-mg Implants

Medium: pH 7.4 phosphate buffered saline prepared as follows. Dissolve 8 g/L of sodium chloride, 0.19 g/L of potassium dihydrogen phosphate, 1.38 g/L of anhydrous disodium hydrogen phosphate, and 0.2 g/L of sodium azide in water. Adjust with 2 M hydrochloric acid to a pH of 7.4. Pass through a sterile filter of NMT 0.2-µm pore size into a sterile container; 50 mL.

Apparatus: 120-mL flat-bottomed, borosilicate glass jar with a tight plastic cap. Incubate at 39 ± 0.5°. [Note—Suitable procedures should be carried out to remove/minimize microbiological contamination on the glassware immediately before the test, e.g., rinse with methanol and dry at 90° for 2 h.]

Times: 72, 336, 840, 1344, and 2016 h

Sample solutions: Transfer 50 mL of *Medium* to the jars, seal, and warm to 39 ± 0.5° overnight in the incubator. Place a single Implant in each jar, and return to the incubator. At the times specified, remove the jars from the incubator, swirl gently to mix, and withdraw 5 mL of aliquot at 24, 72, 168, and 264 h, and 20 mL of aliquot at 336, 504, 672, 840, 1008, 1176, 1344, 1512, 1680, 1848, and 2016 h. Replace the aliquot withdrawn with the same volume of prewarmed *Medium* into the jar, and return to the incubator. [Note—At each sampling time point, the UV absorbance must be measured so that the goserelin content of the test aliquot can be used in the calculation of cumulative release.]

Standard solution: 0.1 mg/mL of USP Goserelin Acetate RS in *Medium*

Analytical wavelength: 280 nm

[Note—Bandwidth is 10 nm.]

Path length cell: 1 cm

Blank: *Medium*

Analysis

Samples: *Sample solutions* and *Standard solution*

Calculate each *Sample solution* concentration of goserelin taken at each sampling time point, C_x:

$$\text{Result} = (A_U/A_S) \times C_S$$

A_U = absorbance of each *Sample solution* taken at each sampling time point

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Goserelin Acetate RS in the *Standard solution* (mg/mL)

Calculate the cumulative amount of goserelin ($C_{59}H_{84}N_{18}O_{14}$) dissolved, as a percentage of the labeled amount of the dose, at the specified times:

$$\text{Result} = \frac{\left[\left(C_X \times V_0 \times D\right) + \Sigma_{n=1}^{x-1}\left(C_n \times V_n \times D\right)\right]}{W} \times 100$$

C_x = concentration of goserelin in each *Sample solution* taken at each sampling time point (mg/mL)

V_0 = volume of the dissolution *Medium*, 50 mL

D = dilution factor

C_n = concentration of goserelin in each *Sample solution* taken at n sampling time point (mg/mL), n must be ≤ x−1

V_n = volume of each *Sample solution* taken at n sampling time point (mL)

W = amount of goserelin in the sample (mg)

Tolerances: See *Table 1*.

Table 1

Time (h)	For 3.6-mg Implants Only Amount Dissolved (%)	For 10.8-mg Implants Only Amount Dissolved (%)	
	Each of the Three Replicates (Individually)	Mean of the 6 Implants	Individual Implant
72	—	10–25	5–30
168	NMT 20	—	—
336	25–55	15–40	10–45
408	35–75	—	—
504	65–90	—	—
672	85–105	—	—
840	—	20–55	15–60
1344	—	60–85	55–90
2016	—	NLT 75	NLT 70

- **Uniformity of Dosage Units ⟨905⟩**

Mobile phase: 2.72 mg/mL of potassium dihydrogen phosphate in a mixture of water and methanol (45:55). Adjust with phosphoric acid to a pH of 3.0.

Diluent: Acetonitrile and water (85:15)

Standard solution: 0.2 mg/mL of USP Goserelin Acetate RS in *Diluent*

Sample solution: Nominally 0.2 mg/mL of goserelin in *Diluent* prepared by dissolving 1 Implant in a suitable volume of *Diluent* with the aid of sonication

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 35°

Flow rate: 1.8 mL/min

Injection volume: 10 µL

Run time: 12 min

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5 for the goserelin peak

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

r_U = peak response of goserelin from the *Sample solution*

r_S = peak response of goserelin from the *Standard solution*

C_S = concentration of USP Goserelin Acetate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of goserelin in the *Sample solution* (mg/mL)

Acceptance criteria: Meet the requirements

PRODUCT-RELATED SUBSTANCES AND IMPURITIES

• **Procedure 1**

Mobile phase: 2.72 mg/mL of potassium dihydrogen phosphate in a mixture of acetonitrile and water (27:73). Adjust with phosphoric acid to a pH of 3.0.

Diluent: Acetonitrile and water (85:15)

System suitability solution: 20 µg/mL each of USP Goserelin Acetate RS and USP Goserelin Related Compound A RS in *Diluent*

Sensitivity solution: 3 µg/mL of USP Goserelin Acetate RS in *Diluent*

Standard solution: 20 µg/mL of USP Goserelin Acetate RS in *Diluent*

Sample solution: Nominally 2.0 mg/mL of goserelin prepared by dissolving 10 Implants in *Diluent* with the aid of sonication

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1.8 mL/min

Injection volume: 5 µL

Run time: 60 min

System suitability

Samples: *System suitability solution*, *Sensitivity solution*, and *Standard solution*

[Note—The retention times for goserelin related compound A and goserelin in the *System suitability solution* are approximately 17 and 22 min, respectively.]

Suitability requirements

Resolution: NLT 4.5 between the main goserelin and goserelin related compound A peaks, *System suitability solution*

Tailing factor: NMT 2.0 for the goserelin peak, *Standard solution*

Relative standard deviation: NMT 4.5%, *Standard solution*

Signal-to-noise ratio: NLT 5, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Implants taken:

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

r_U = peak response of any individual impurity from the *Sample solution*

r_S = peak response of goserelin from the *Standard solution*

C_S = concentration of USP Goserelin Acetate RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of goserelin in the *Sample solution* (mg/mL)

F = conversion factor, 0.1

Acceptance criteria

Any individual impurity: NMT 1.0%

Total impurities: NMT 4.0% from *Procedure 1*

- **Procedure 2**

Buffer, Mobile phase, Diluent, System suitability solution, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Sensitivity solution: 6.5 µg/mL of USP Goserelin Acetate RS in *Diluent*

Peak identification solution: Degrade Implants at 90° for 4 h. Dissolve the degraded Implants in *Diluent* with the aid of sonication to obtain a solution that contains approximately 2 mg/mL of goserelin.

System suitability

Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*

Suitability requirements

Resolution: NLT 4.0 between the main goserelin and goserelin related compound A peaks, *System suitability solution*

Tailing factor: NMT 1.5 for the goserelin peak, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Signal-to-noise ratio: NLT 5, *Sensitivity solution*

Analysis

Samples: *Standard solution*, *Sample solution*, and *Peak identification solution*

Identify the *O*-glycolyl-ser^4-goserelin and polymer envelope peaks using the chromatogram of the *Peak identification solution* and the relative retention times listed in *Table 2*.

Calculate the percentage of any individual impurity in the portion of Implants taken:

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

r_U = peak response of any individual impurity from the *Sample solution*

r_S = peak response of goserelin from the *Standard solution*

C_S = concentration of USP Goserelin Acetate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of goserelin in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Polymer envelope[a]	0.10–0.60	5.5
O-Glycolyl-ser^4-goserelin	0.93	2.0
Any unspecified impurity	—	1.0
Total impurities[b]	—	10.0

[a] *O*-Lactide/glycolide copolymer chain to ser^4 of goserelin. It is calculated as the sum of all peaks eluted in the specified relative retention time range.

[b] Total impurities is the sum of impurities from *Procedure 2* and impurity C from *Procedure 3*.

- **Procedure 3**

[Note—Perform this test if impurity C is present.]

Buffer: Prepare as directed in the *Assay*.

Mobile phase: Acetonitrile and *Buffer* (87.5:12.5)

Diluent: Acetonitrile and water (85:15)

System suitability solution: Weigh 4 mg of USP Goserelin Acetate RS, add 250 µL of trifluoroacetic acid, and leave to stand for 24 h. Dissolve in 20 mL of *Diluent* to obtain a solution containing goserelin related compound B. [NOTE—Goserelin related compound B is des-*t*-butyl-goserelin.]

Sensitivity solution: 3 µg/mL of USP Goserelin Acetate RS in *Diluent*

Standard solution: 20 µg/mL of USP Goserelin Acetate RS in *Diluent*

Sample solution: Nominally 2.0 mg/mL of goserelin in *Diluent* prepared by adding 10 Implants to a suitable volumetric flask. Add *Diluent* to about 70% of the total volume, and sonicate to dissolve the sample. Cool to room temperature, and dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 7.8-mm × 30-cm; 5-µm packing L33

Flow rate: 2.0 mL/min

Injection volume: 50 µL

Run time: 30 min

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

Suitability requirements

Retention: The retention time for goserelin related compound B is between 19 and 24 min, *System suitability solution*

Signal-to-noise ratio: NLT 5, *Sensitivity solution*

Analysis

Samples: *System suitability solution*, *Standard solution*, and *Sample solution*

Identify the impurity C peak with a retention time relative to goserelin related compound B of 1.1 using the chromatogram of the *System suitability solution*. [NOTE—Impurity C is a specified, but unidentified, impurity.]

Calculate the percentage of impurity C in the portion of Implants taken:

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

r_U = peak response of impurity C from the *Sample solution*

r_S = peak response of goserelin from the *Standard solution*

C_S = concentration of USP Goserelin Acetate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of goserelin in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 1.0%

OTHER COMPONENTS

• **ACETIC ACID CONTENT**

Standard stock solution: 6.25 mg/mL of USP Glacial Acetic Acid RS in dimethylformamide

Internal standard stock solution: Transfer 1.0 mL of *n*-hexadecane to a 50-mL volumetric flask containing approximately 30 mL of dimethylformamide. Dilute with dimethylformamide to volume.

Standard solution: Transfer 10.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, and add approximately 50 mL of dimethylformamide. Add 5.0 mL of the *Internal standard stock solution*, and dilute with dimethylformamide to volume.

Sample solution: Weigh 150 mg of Implants into a 5-mL volumetric flask. Add approximately 1 mL of dimethylformamide and sonicate to dissolve. Add 250 µL of the *Internal standard stock solution*, and dilute with dimethylformamide to volume.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.32-mm × 10-m; fused-silica capillary that contains a 0.3-µm film of phase G35

Temperatures

Injection port: 200°

Column: See *Table 3*.

Table 3

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	0.1
50	30	200	3

Detector: 250°

Carrier gas: Helium

Flow rate: 1.3 mL/min

Injection volume: 1 µL

Split ratio: 100:30

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 15 between acetic acid and *n*-hexadecane

Tailing factor: NMT 2.0 for acetic acid

Relative standard deviation: NMT 6% for the response ratio of acetic acid to *n*-hexadecane

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of acetic acid in the portion of Implants taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of acetic acid to *n*-hexadecane from the *Sample solution*

R_S = peak response ratio of acetic acid to *n*-hexadecane from the *Standard solution*

C_S = concentration of USP Glacial Acetic Acid RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of the goserelin implant sample in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 2.5%

SPECIFIC TESTS

- **Water Determination ⟨921⟩, *Method I, Method Ic***

Sample solution: 27-mg/mL solution of Implant in dry dimethylformamide

Analysis: Determine the water content of 1.0-mL of the *Sample solution*. Perform a blank determination and make any necessary correction.

Acceptance criteria: NMT 2.5%

- **Bacterial Endotoxins Test ⟨85⟩:** NMT 350 USP Endotoxin Units/Implant
- **Sterility Tests ⟨71⟩, *Test for Sterility of the Product to be Examined, Membrane Filtration*:** Meet the requirements

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed, tight, light-resistant single-unit containers at controlled room temperature.
- **Labeling:** The label states the amount of the peptide (goserelin) in mg in each implant.
- **USP Reference Standards ⟨11⟩**

USP Glacial Acetic Acid RS
USP Endotoxin RS
USP Goserelin Acetate RS
USP Goserelin Related Compound A RS
4-D-Serine goserelin.

Topic/Question	Contact	Expert Committee
GOSERELIN IMPLANTS	Ying Han Associate Science & Standards Liaison	BIO12020 Biologics Monographs 1 - Peptides

Chromatographic Database Information: Chromatographic Database

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