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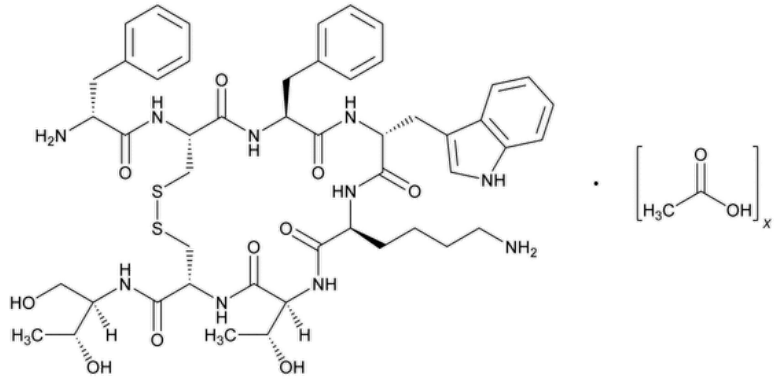
# Octreotide Acetate



$C_{49}H_{66}N_{10}O_{10}S_2 \cdot xC_2H_4O_2$ 1019 (as free base)

L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-*N*-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2→7)-disulfide, [*R*-(*R**,*R**)]-, acetate (salt);

D-Phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (2→7)-disulfide acetate (salt);

D-Phenylalanyl-L-hemicystyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-hemicystyl-L-threoninol cyclic (2→7)-disulfide acetate (salt) CAS RN®: 79517-01-4; UNII: 75R0U2568I.

**DEFINITION**

Octreotide Acetate is a long-acting synthetic octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. It contains NLT 95.0% and NMT 105.0% of octreotide ($C_{49}H_{66}N_{10}O_{10}S_2$), calculated on the anhydrous, acetic acid-free basis.

**IDENTIFICATION**

• **A. HPLC**

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

**Identification sample solution:** Mix an equal volume of the *Standard solution* and the *Sample solution*.

**Analysis**

**Samples:** *Identification sample solution, Standard solution,* and *Sample solution*

Examine the chromatograms of the *Identification sample solution*, *Standard solution*, and *Sample solution*.

**Acceptance criteria:** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, and the major peak of the *Identification sample solution* elutes as a single peak.

• **B. Amino Acid Analysis**

[Note—The following method is given for informational purposes; any validated amino acid analysis method can be used.]

**Diluent:** 0.1 M hydrochloric acid

**Standard amino acid mixture:** 2500 nmol/mL each of *Lys*, *His*, $NH_3$, *Arg*, *Asp*, *Thr*, *Ser*, *Glu*, *Pro*, *Gly*, *Ala*, *Val*, *Met*, *Ile*, *Leu*, *Tyr*, *Phe*, and 1250 nmol/mL of *Cys-Cys* in *Diluent*

**Standard tryptophan solution:** 0.2042 mg/mL of tryptophan in *Diluent*. This solution contains 1000 nmol/mL of *Trp*.

**Standard threonin-ol solution:** 0.1052 mg/mL of *Thr-ol* in *Diluent*. This solution contains 1000 nmol/mL *Thr-ol*. [Note—1000 nmol/mL = 1 mM]

**Standard solution:** *Diluent*, *Standard amino acid mixture*, *Standard tryptophan solution*, and *Standard threonin-ol solution* (76:4:10:10). The concentration is 100.0 nmol/mL for each amino acid.

**Sample solution A:** Weigh 1.00–1.50 mg of Octreotide Acetate into a 5-mL ampule. Add 1000 µL of *Diluent* and 1.2 mL of 30% (w/w) hydrochloric acid, cool the ampule in dry ice, evacuate, and seal by melting. Heat the ampule for 16 h at 115°. Allow to cool and transfer the

contents of the ampule quantitatively into a 25-mL round-bottomed flask, rinse with *Diluent*, and evaporate to dryness on a rotary evaporator. Dissolve the residue in 10.00 mL of *Diluent*.

**Sample solution B:** Weigh 1.00–1.50 mg of Octreotide Acetate into a 5-mL ampule. Add 1000 µL of *Diluent* and 1.2 mL of 30% (w/w) hydrochloric acid with 1% (v/v) thioglycolic acid, cool the ampule in dry ice, evacuate, and seal by melting. Heat the ampule for 16 h in a heating block at 115°. Allow to cool and transfer the contents of the ampule quantitatively into a 25-mL round-bottomed flask, rinse with *Diluent*, and evaporate to dryness on a rotary evaporator. Dissolve the residue in 10.00 mL of *Diluent*.

**Analysis**

**Samples:** *Standard solution*, *Sample solution A*, and *Sample solution B*

Standardize the instrument with the *Standard solution*. Inject a suitable volume of *Standard solution*, *Sample solution A*, and *Sample solution B*. Evaluate the peak areas of each amino acid found in relation to the peak areas of the respective amino acids in the *Standard solution*, express the content of each amino acid in nmoles.

Calculate *A*, the average number of nmoles of the amino acids found to be stable under hydrolysis conditions (three stable amino acids—2 *Phe* and 1 *Lys*) taken:

$$A = N_T/3$$

$N_T$ = total nmoles of the stable amino acids

Calculate the ratio of the amino acids taken:

$$\text{Result} = N_E/A$$

$N_E$ = nmoles of each amino acid

[NOTE—For *Trp* use only data obtained with *Sample solution B*. For *Cys* use only data obtained with *Sample solution A*.]

**Acceptance criteria:** See *Table 1*.

**Table 1**

| Name | Acceptance Criteria |
|---|---|
| *Thr* | 0.7–1.1 |
| *Lys* | 0.9–1.3 |
| *Phe* | 1.8–2.2 |
| *Trp* | 0.4–1.1 |
| *Cys* | 1.0–2.2 |
| *Thr-ol* | 0.6–1.3 |

## ASSAY

• **PROCEDURE**

**Solution A:** 0.02% (v/v) of trifluoroacetic acid in water

**Solution B:** Acetonitrile

**Mobile phase:** See *Table 2*.

**Table 2**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 90 | 10 |
| 25 | 65 | 35 |
| 30 | 10 | 90 |

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 35 | 10 | 90 |
| 40 | 90 | 10 |
| 45 | 90 | 10 |

**System suitability solution:** 0.5 mg/mL of USP Octreotide Acetate RS and 0.2 mg/mL of USP Octreotide Non-Cyclic System Suitability Marker RS in *Solution A*

**Standard solution:** 0.5 mg/mL of USP Octreotide Acetate RS in *Solution A*

**Sample solution:** 0.5 mg/mL of Octreotide Acetate in *Solution A*. [NOTE—Place Octreotide Acetate in a desiccator containing saturated sodium chloride solution for at least 30 min before weighing. Determine the water content by suitable analysis.]

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 25-cm; 4-µm packing L87

**Column temperature:** 40°

**Flow rate:** 1 mL/min

**Injection volume:** 10 µL

**System suitability**

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

[NOTE—The retention times for octreotide and non-cyclic octreotide in the *System suitability solution* are about 16.5 and 18.5 min, respectively.]

**Suitability requirements**

**Resolution:** NLT 2.0 between octreotide and non-cyclic octreotide, *System suitability solution*

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

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of octreotide ($C_{49}H_{66}N_{10}O_{10}S_2$) in the portion of Octreotide Acetate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times [100/(100 - W - Ac)] \times 100$$

$r_U$ = peak response of octreotide from the *Sample solution*

$r_S$ = peak response of octreotide from the *Standard solution*

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

$C_U$ = concentration of Octreotide Acetate in the *Sample solution* (mg/mL)

$W$ = water content in the Octreotide Acetate sample (%)

$Ac$ = acetic acid content in the Octreotide Acetate sample (%)

**Acceptance criteria:** 95.0%–105.0% on the anhydrous, acetic acid-free basis

## OTHER COMPONENTS

• **ACETIC ACID IN PEPTIDES ⟨503⟩:** 5.0%–12.8%

## PRODUCT-RELATED SUBSTANCES AND IMPURITIES

• **OCTREOTIDE ACETATE RELATED COMPOUNDS**

[NOTE—Manufacturers should determine the suitability of their related substances method for their process-related and degradation impurities. For any impurity peak above the limit for unspecified impurity peaks, identification and appropriate qualification is required.]

**Solution A, Solution B, Mobile phase, System suitability solution, Sample solution, Chromatographic system,** and **System suitability:** Proceed as directed in the *Assay*.

**Analysis**

**Sample:** *Sample solution*

Calculate the percentage of each impurity taken, disregarding any peak with a retention time of less than 5 min and any peak with an area less than 0.1% of the main peak:

$$\text{Result} = (r_U/r_T) \times 100$$

$r_U$ = peak response of each impurity from the *Sample solution*

$r_T$ = sum of the peak responses from the *Sample solution*, excluding those of the solvent peaks

**Acceptance criteria:** See *Table 3*.

**Table 3**

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|---|---|---|
| Acetyl-Lys$^5$-octreotide[a] | 1.4 | 0.5 |
| Acetyl-Phe$^1$-octreotide[b] | 1.5 | 0.5 |
| Unspecified impurity | — | 0.5 |
| Total impurities | — | 2.0 |

[a] D-Phenylalanyl-L-hemicystyl-L-phenylalanyl-D-tryptophyl-(*N*-acetyl)-L-lysyl-L-threonyl-L-hemicystyl-L-threoninol cyclic (2→7)-disulfide.

[b] (*N*-Acetyl)-D-Phenylalanyl-L-hemicystyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-hemicystyl-L-threoninol cyclic (2→7)-disulfide.

**PROCESS-RELATED IMPURITIES**

• **Trifluoroacetic Acid (TFA) in Peptides ⟨503.1⟩:** NMT 0.25%.

[Note—Perform this test if trifluoroacetic acid is used in the manufacturing process.]

**SPECIFIC TESTS**

• **Water Determination ⟨921⟩, *Method I*:** NMT 10.0%

• **Bacterial Endotoxins Test ⟨85⟩:** NMT 466 USP Endotoxin Units/mg of octreotide acetate

• **Microbial Enumeration Tests ⟨61⟩ and Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count is NMT 100 cfu/g. The total yeast and mold count is NMT 100 cfu/g.

**ADDITIONAL REQUIREMENTS**

• **Packaging and Storage:** Preserve in air-tight containers. Store at a temperature of 2°–8°, protected from light.

• **USP Reference Standards ⟨11⟩**

USP Endotoxin RS

USP Octreotide Acetate RS

USP Octreotide Non-Cyclic System Suitability Marker RS



**Auxiliary Information** - Please check for your question in the FAQs before contacting USP.

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| OCTREOTIDE ACETATE | Ying Han<br>Associate Science & Standards Liaison | BIO12020 Biologics Monographs 1 - Peptides |
| REFERENCE STANDARD SUPPORT | RS Technical Services<br>RSTECH@usp.org | BIO12020 Biologics Monographs 1 - Peptides |

**Chromatographic Database Information:** Chromatographic Database

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