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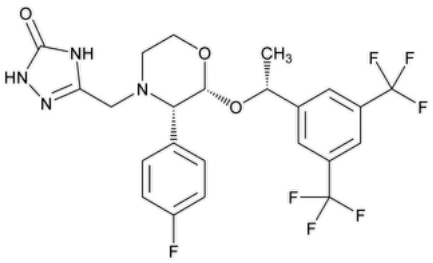
Aprepitant



$C_{23}H_{21}F_7N_4O_3$ 534.43

3*H*-1,2,4-Triazol-3-one, 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-; 3-[[(2*R*,3*S*)-3-(*p*-Fluorophenyl)-2-[[(α*R*)-α-methyl-3,5-bis(trifluoromethyl)benzyl]oxy]morpholino]methyl]-Δ^2-1,2,4-triazolin-5-one; 3-[[(2*R*,3*S*)-2-[(*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)morpholino]methyl]-1*H*-1,2,4-triazol-5(4*H*)-one; 5-[[(2*R*,3*S*)-2-[(*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one CAS RN®: 170729-80-3; UNII: 1NF15YR6UY.

DEFINITION

Aprepitant contains NLT 98.0% and NMT 102.0% of aprepitant ($C_{23}H_{21}F_7N_4O_3$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A, 197K, or 197M▲ (CN 1-May-2020)

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

ASSAY

• **Procedure**

Dilute phosphoric acid: Dilute 1 mL of phosphoric acid with water to 1 L.

Mobile phase: Acetonitrile and *Dilute phosphoric acid* (48:52)

Diluent: Acetonitrile and *Dilute phosphoric acid* (50:50)

Standard solution: 0.2 mg/mL of USP Aprepitant RS in *Diluent*; sonicate as needed

Sample solution: 0.2 mg/mL of Aprepitant in *Diluent*; sonicate as needed

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

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

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of aprepitant ($C_{23}H_{21}F_7N_4O_3$) in the portion of Aprepitant 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: 98.0%–102.0%, on the anhydrous and solvent-free basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

• **Organic Impurities**

Dilute phosphoric acid and **Diluent:** Proceed as directed in the *Assay*.

Solution A: *Dilute phosphoric acid*

Solution B: Acetonitrile

Mobile phase: See *Table 1.*

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	58	42
25	58	42
45	30	70
50	30	70

Return to original conditions and re-equilibrate the system.

System suitability solution: 2.0 mg/mL of USP Aprepitant RS and 0.003 mg/mL of USP Desfluoro Aprepitant RS in *Diluent*, using sonication as necessary to dissolve

Sensitivity solution: 0.001 mg/mL of USP Aprepitant RS in *Diluent*

Standard solution: 0.003 mg/mL of USP Aprepitant RS in *Diluent*, using sonication as necessary to dissolve

Sample solution: 2.0 mg/mL of Aprepitant in *Diluent*, using sonication as necessary to dissolve

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

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

Column temperature: 35°

Flow rate: 1.0 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 3.0 between the desfluoro aprepitant and aprepitant peaks, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of Aprepitant taken:

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

r_U = peak response for each impurity from the *Sample solution*

r_S = peak response for aprepitant from the *Standard solution*

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

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

Acceptance criteria: See *Table 2*. Disregard any peak below 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Desfluoro aprepitant	0.85	0.15
Aprepitant	1.0	—
Any individual unspecified impurity	—	0.10
Total impurities	—	0.30

• **Limit of *S,R,S*-Enantiomer** (if present)

[Note—Perform this test if this impurity is possible from the manufacturing process.]

Mobile phase: Hexane and dehydrated alcohol (90:10)

System suitability solution: 0.08 mg/mL of USP Aprepitant RS and 0.08 mg/mL of USP Aprepitant Related Compound B RS in *Mobile phase*

Sample solution: 0.5 mg/mL of Aprepitant in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; packing L51

Column temperature: 30°

Flow rate: 0.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: Greater than 2.0 between the enantiomer peaks. [Note—The elution order is the *S,R,S*-enantiomer followed by the aprepitant peak, which is the *R,S,R*-enantiomer.]

Analysis

Sample: *Sample solution*

Calculate the percentage of the *S,R,S*-enantiomer in the portion of Aprepitant taken:

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

r_U = peak response of the *S,R,S*-enantiomer

r_T = sum of the peak responses of aprepitant and the *S,R,S*-enantiomer

Acceptance criteria: NMT 0.10% of the *S,R,S*-enantiomer

SPECIFIC TESTS

• **Water Determination,** *Method Iaor Ic*⟨921⟩**:** NMT 0.5%

• **Optical Rotation,** *Specific Rotation*⟨781S⟩

Sample solution: 10 mg/mL in methanol

Acceptance criteria: +66.0° to +71.0°

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers, protected from light. Store at room temperature.

• **USP Reference Standards** ⟨11⟩

USP Aprepitant RS

USP Aprepitant Related Compound B RS

S,R,S-Enantiomer: 3-[[(2*S*,3*R*)-2-[(*S*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)morpholino]methyl]-1*H*-1,2,4-triazol-5(4*H*)-one.

$C_{23}H_{21}F_7N_4O_3$ 534.43

USP Desfluoro Aprepitant RS

5-[[(2*R*,3*S*)-2-[(*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3-phenylmorpholino]methyl]-2*H*-1,2,4-triazol-3(4*H*)-one.

$C_{23}H_{22}F_6N_4O_3$ 516.44

Topic/Question	Contact	Expert Committee
APREPITANT	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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