

BRIEFING

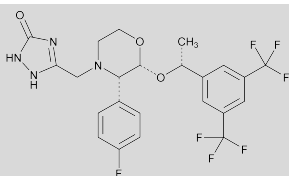
Aprepitant. A new USP Pending Monograph is being proposed based on validated methods of analysis. The HPLC procedures in the *Assay* and the test for *Organic Impurities* are based on analyses performed with the Hypersil BDS C8 brand of L7 column. The typical retention time for the aprepitant peak is 14 min. The HPLC procedure in the test for *Enantiomeric Purity* is based on analysis performed with the Chiralpak AD-H brand of L51 column. The typical retention time for aprepitant is 15 min.
Reagents: Orthophosphoric acid (phosphoric acid, crystalline), H₃PO₄—98.00 [7664-38-2]—Use a suitable grade with a content of NLT 98%.

(SM3: E. Gonikberg.)
Correspondence Number—C89258

Add the following:

▶Aprepitant

Draft 1



C₂₃H₂₁F₇N₄O₃ 534.43
3*H*-1,2,4-Triazol-3-one, 5-[[*(2R,3S)*-2-[[*(1R)*-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-;
3-[[*(2R,3S)*-3-(*p*-Fluorophenyl)-2-[[*(αR)*-*α*-methyl-3,5-bis(trifluoromethyl)benzyl]oxy]morpholino]methyl]-*Δ*²-1,2,4-triazolin-5-one;
3-[[*(2R,3S)*-2-[[*(R)*-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)morpholino]methyl]-1*H*-1,2,4-triazol-5(4*H*)-one [170729-80-3].

DEFINITION

Aprepitant contains NLT 98.0% and NMT 102.0% of C₂₃H₂₁F₇N₄O₃, calculated on the anhydrous basis.

IDENTIFICATION

- A. INFRARED ABSORPTION (197K)**
- 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**
Buffer: Dissolve 1.96 g of orthophosphoric acid and 0.34 g of tetrabutylammonium hydrogen sulfate in 1000 mL of water.
Solution A: Acetonitrile and *Buffer* (20:80)
Solution B: Acetonitrile and *Buffer* (80:20)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	65	35
5	65	35
35	20	80
50	20	80
52	65	35
60	65	35

Diluent: Acetonitrile and water (1:1)
Standard solution: 0.05 mg/mL of USP Aprepitant RS in *Diluent*
Sample solution: 0.05 mg/mL of Aprepitant in *Diluent*
Chromatographic system
(See *Chromatography* (621), *System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 15-cm; 5- μ m packing L7
Flow rate: 1 mL/min
Injection size: 20 μ L
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 1.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of aprepitant (C₂₃H₂₁F₇N₄O₃) 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 basis

IMPURITIES

- RESIDUE ON IGNITION (281):** NMT 0.1%
- HEAVY METALS, Method II (231):** NMT 10 ppm
- ORGANIC IMPURITIES**
Buffer, Solution A, Solution B, Diluent, Mobile phase, and Chromatographic system: Proceed as directed in the *Assay*.
Sample solution: 1 mg/mL of Aprepitant in *Diluent*
System suitability solution: 1 mg/mL of USP Aprepitant RS and 0.05 mg/mL of USP Aprepitant Related Compound A RS in *Diluent*
System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 2.0 between the aprepitant and aprepitant related compound A peaks
Tailing factor: NMT 2.0 for the aprepitant peak
Analysis
Sample: *Sample solution*
Calculate the percentage of any individual impurity in the portion of Aprepitant taken:

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

r_U = peak response of each impurity
r_T = sum of all the peak responses
Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Aprepitant	1.0	—
<i>R,R,R</i> -Diastereomer ^a	1.15	0.15
Any other individual impurity	—	0.10
Total impurities	—	0.50

^a USP Aprepitant Related Compound A RS.

ENANTIOMERIC PURITY

- 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*.)

2 / Aprepitant

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; packing L51

Column temperature: 30°

Flow rate: 0.5 mL/min

Injection size: 20 µL

System suitabilitySample: *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.]

AnalysisSample: *Sample solution*

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

$$\text{Result} = (r_u/r_r) \times 100$$

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

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

Acceptance criteria: NMT 0.15% of the *S,R,S*-enantiomer

SPECIFIC TESTS

- **WATER DETERMINATION, Method 1a (921):** NMT 0.50%

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 A RS

(R,R,R-diastereomer)

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

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USP Aprepitant Related Compound B RS

(S,R,S-enantiomer)

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

C₂₃H₂₁F₇N₄O₃ 534.43◀(1-Sep-2011)