

BRIEFING

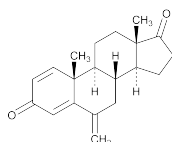
Exemestane. This monograph has been posted on the USP Website for review and public comment for more than 90 days. No comments were received. The SM3 Expert Committee has approved the monograph as an Authorized USP Pending Monograph. Following is further information on the monograph.

1. The monograph uses the flexible monograph approach and includes three *Organic Impurities* procedures suitable for the different synthetic routes. These procedures are tentatively identified as Procedure #, Procedure ##, and Procedure ###; they will be finalized after FDA approves the drug product application(s) in which the drug substance DMF(s) is (are) referenced.
2. A *Labeling* statement will be added as needed.
3. The liquid chromatographic procedures used in the *Assay* and in *Procedure #* are based on analyses performed with the Hypersil BDS C18 brand of L1 column. The typical retention times for exemestane are about 8.5 min in the *Assay* and about 30 min in *Procedure #*.
4. The liquid chromatographic procedure used in *Procedure ##* is based on analyses performed with the Waters XTerra RP18 brand of L1 column. The typical retention time for exemestane is about 23.5 min.
5. The liquid chromatographic procedure used in *Procedure ###* is based on analyses performed with the Daicel Chiralcel OJ brand of L## column. The typical retention time for exemestane is about 17 min.

(SM3: F. Mao.)
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Exemestane

v.1 Authorized January 1, 2011



C₂₀H₂₄O₂ 296.40
Androsta-1,4-diene-3,17-dione, 6-methylene-;
6-Methyleneandrosta-1,4-diene-3,17-dione [107868-30-4].

DEFINITION

Exemestane contains NLT 98.0% and NMT 102.0% of C₂₀H₂₄O₂, 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**
Solution A: Water
Solution B: Acetonitrile
Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	60	40
15	60	40
18	10	90

Time (min)	Solution A (%)	Solution B (%)
28	10	90
30	60	40
35	60	40

Diluent: Acetonitrile and water (1:1)
Standard solution: 0.1 mg/mL of USP Exemestane RS in *Diluent*

Sample solution: 0.1 mg/mL of Exemestane in *Diluent*

Chromatographic system
(See *Chromatography* (621), *System Suitability*.)

Mode: LC
Detector: UV 247 nm
Column: 4.6-mm × 15-cm; 3-μm packing L1
Column temperature: 45°
Flow rate: 1.0 mL/min

Injection size: 10 μL

System suitability
Sample: *Standard solution*

Suitability requirements
Relative standard deviation: NMT 1.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of C₂₀H₂₄O₂ in the portion of Exemestane 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 USP Exemestane RS in the *Standard solution* (mg/mL)
- C_U = concentration of Exemestane in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

Inorganic Impurities

- **RESIDUE ON IGNITION** (281): NMT 0.1%
- **HEAVY METALS, Method II** (231): NMT 10 ppm

Organic Impurities

[NOTE—On the basis of the synthetic route, perform either Procedure # or Procedures ## and ###.]

- **PROCEDURE #** (If exemestane related compound A is specified, Procedure # is performed.)
Diluent and Chromatographic system: Proceed as directed in the *Assay*.
Solution A: Water
Solution B: Methanol
Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	70	30
35	40	60
40	10	90
50	10	90
52	70	30
60	70	30

System suitability solution: 1 mg/mL of USP Exemestane RS and 1.5 μg/mL of USP Exemestane Related Compound A RS in *Diluent*

Standard solution: 1 μg/mL of USP Exemestane RS in *Diluent*

Sample solution: 1 mg/mL of Exemestane in *Diluent*

System suitability
Sample: *System suitability solution*

Suitability requirements
Resolution: Greater than 5.0 between exemestane and exemestane related compound A

2 / Exemestane

Tailing factor: NMT 1.5 for the exemestane peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Exemestane taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

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

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

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

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

F = relative response factor for each individual impurity (see *Impurity Table 1*)

Acceptance criteria

Individual impurities: See *Impurity Table 1*. [NOTE—Disregard any impurity peaks less than 0.05%.]

Total impurities: NMT 0.50%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Spirooxiran 1 ^a	0.54	1.0	0.15
Spirooxiran 2 ^a	0.61	1.1	0.15
Exemestane related compound C ^b	0.80	1.1	0.15
Exemestane	1.0	—	—
Exemestane related compound A ^c	1.12	0.65	0.15
Any unspecified impurity	—	1.0	0.10

^a 6 α /6 β -Spirooxiran-androsta-1,4-diene-3,17-dione; spirooxiran 1 and spirooxiran 2 are diastereomers.

^b Androsta-1,4-diene-3,17-dione.

^c 6-Methyleneandrosta-4-ene-3,17-dione.

- **PROCEDURE ##** (If exemestane related compound B and exemestane related compound D are specified, Procedures ## and ### are performed.)

Solution A: Water

Solution B: Acetonitrile

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	75	25
30	55	45
40	5	95
45	5	95
45.1	75	25

Diluent: Acetonitrile and water (3:1)

System suitability solution: 1 mg/mL of USP Exemestane RS, 0.01 mg/mL of USP Exemestane Related Compound B RS, and 0.01 mg/mL of USP Exemestane Related Compound C RS in *Diluent*

Standard solution: 5 μ g/mL of USP Exemestane RS in *Diluent*

Sensitivity solution: 0.5 μ g/mL each of USP Exemestane RS, USP Exemestane Related Compound B RS, and USP Exemestane Related Compound C RS in *Diluent*

Sample solution: 1 mg/mL of Exemestane in *Diluent*.

[NOTE—The concentration of the *Sample solution* is calculated on the anhydrous basis.]

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 247 nm

Column: 4.6-mm \times 25-cm; 3.5- μ m packing L1

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection size: 10 μ L

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between exemestane related compound B and exemestane related compound C; NLT 2.0 between exemestane related compound C and exemestane, *System suitability solution*

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

Signal-to-noise ratio: NLT 10 for the exemestane, exemestane related compound B, and exemestane related compound C peaks, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Exemestane taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

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

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

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

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

F = relative response factor for each individual impurity (see *Impurity Table 2*)

Acceptance criteria

Individual impurities: See *Impurity Table 2*. [NOTE—Disregard any impurity peaks less than 0.05%.]

Impurity Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Exemestane related compound B ^a	0.34	0.95	0.1
Exemestane related compound C ^b	0.77	1.1	0.15
Exemestane	1.0	—	—
Any unspecified impurity	—	1.0	0.10

^a 6-Hydroxymethylandrosta-1,4-diene-3,17-dione.

^b Androsta-1,4-diene-3,17-dione.

- **PROCEDURE ###: LIMIT OF EXEMESTANE RELATED COMPOUND D** (If exemestane related compound B and exemestane related compound D are specified, Procedures ## and ### are performed.)

Mobile phase: Hexane, isopropyl alcohol, and diethylamine (90:10:0.1)

Standard solution: 0.04 mg/mL of USP Exemestane RS in anhydrous alcohol

System suitability solution: 8 mg/mL of USP Exemestane System Suitability Mixture RS in anhydrous alcohol

Sensitivity solution: 4 μ g/mL of USP Exemestane RS in anhydrous alcohol, from the *Standard solution*

Sample solution: 8 mg/mL of Exemestane in anhydrous alcohol. [NOTE—The concentration of the *Sample solution* is calculated on the anhydrous basis.]

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC
 Detector: UV 247 nm
 Column: 4.6-mm × 25-cm; 10-μm packing L##
 Column temperature: 30°
 Flow rate: 1.2 mL/min
 Injection size: 10 μL

System suitability

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

Suitability requirements

Resolution: NLT than 2.0 between exemestane and exemestane related compound D, *System suitability solution*

Relative standard deviation: NMT 5%, *Standard solution*

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

Analysis

Samples: *Standard solution and Sample solution*
 Calculate the percentage of exemestane related compound D in the portion of Exemestane taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times (1/F) \times 100$$

- r_u = peak response of exemestane related compound D from the *Sample solution*
- r_s = peak response of exemestane from the *Standard solution*
- C_s = concentration of USP Exemestane RS in the *Standard solution* (mg/mL)
- C_u = concentration of Exemestane in the *Sample solution* (mg/mL)
- F = relative response factor for exemestane related compound D (see *Impurity Table 3*)

Acceptance criteria

Individual impurities: See *Impurity Table 3*.

Total impurities: NMT 1.0%. [NOTE—Total impurities include the impurities in *Impurity Table 2* and *Impurity Table 3*.]

Impurity Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Exemestane	1.0	1.0	—

^a 16-Methyleneandrosta-1,4-diene-3,17-dione.

Impurity Table 3 (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Exemestane related compound D ^a	1.55	1.1	0.1

^a 16-Methyleneandrosta-1,4-diene-3,17-dione.

SPECIFIC TESTS

- **WATER DETERMINATION, Method I (921):** NMT 0.5%
- **SPECIFIC ROTATION (781S):** +290° to +300°, calculated on the anhydrous basis.
Sample solution: 10 mg/mL in methanol

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at controlled room temperature.
- **LABELING:** [To come]
- **USP REFERENCE STANDARDS (11)**
 - USP Exemestane RS
 - USP Exemestane Related Compound A RS
6-Methyleneandrosta-4-ene-3,17-dione.
C₂₀H₂₆O₂ 298.42
 - USP Exemestane Related Compound B RS
6-Hydroxymethylandrosta-1,4-diene-3,17-dione.
C₂₀H₂₆O₃ 314.42
 - USP Exemestane Related Compound C RS
Androsta-1,4-diene-3,17-dione.
C₁₉H₂₄O₂ 284.39
 - USP Exemestane System Suitability Mixture RS—USP Exemestane System Suitability Mixture RS is exemestane containing a small amount of exemestane related compound D.