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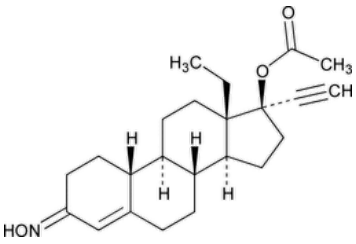
Norgestimate

Change to read:



$C_{23}H_{31}NO_3$ ▲369.51▲ (IRA 1-Aug-2024)

18,19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17α)-(+)-;

(+)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime acetate (ester) CAS RN®: 35189-28-7; UNII: C291HFX4DY.

DEFINITION

Norgestimate is a mixture of (*E*)- and (*Z*)-isomers having a ratio of (*E*)- to (*Z*)-isomer between 1.27 and 1.78, and it contains NLT 98.0% and NMT 102.0% of norgestimate ($C_{23}H_{31}NO_3$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** ▲197A or▲ (IRA 1-Aug-2024) 197K

▲▲ (IRA 1-Aug-2024)

Change to read:

• **B.** The retention ▲times of the major peaks for the (*E*)- and (*Z*)-isomers of the *Sample solution* correspond to those▲ (IRA 1-Aug-2024) of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

• **Procedure**

Diluent: Methanol and water (80:20)

Mobile phase: Tetrahydrofuran, acetonitrile, and water (22:18:60)

Standard solution: 0.5 mg/mL of USP Norgestimate RS in *Diluent*

▲▲ (IRA 1-Aug-2024)

Sample solution: 0.5 mg/mL of Norgestimate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 244 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 25 µL

▲**Run time:** NLT 1.5 times the retention time of (*E*)-norgestimate▲ (IRA 1-Aug-2024)

System suitability

Sample: *Standard solution* ▲▲ (IRA 1-Aug-2024)

[NOTE— ▲See *Table 1* for the relative retention times for (*Z*)-norgestimate and (*E*)-norgestimate.▲ (IRA 1-Aug-2024)]

Suitability requirements

Resolution: NLT 1.5 between (*Z*)-norgestimate and (*E*)-norgestimate

Tailing factor: NMT 1.5 for (*E*)-norgestimate and (*Z*)-norgestimate

Relative standard deviation: NMT ▲0.73%▲ (IRA 1-Aug-2024) for the ▲sum of the peak responses of▲ (IRA 1-Aug-2024) (*E*)-norgestimate and (*Z*)-norgestimate

▲▲ (IRA 1-Aug-2024)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of norgestimate ($C_{23}H_{31}NO_3$) in the portion of Norgestimate taken:

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

r_U = sum of the peak ▲responses▲ (IRA 1-Aug-2024) of (*Z*)-norgestimate and (*E*)-norgestimate from the *Sample solution*

r_S = sum of the peak ▲responses▲ (IRA 1-Aug-2024) of (*Z*)-norgestimate and (*E*)-norgestimate from the *Standard solution*

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

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

Calculate the percentages of the (*Z*)- and (*E*)-isomers, U_Z and U_E, respectively, in the portion of Norgestimate taken:

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

r_U = peak response of ▲(*Z*)-norgestimate and (*E*)-norgestimate▲ (IRA 1-Aug-2024) from the *Sample solution*

r_S = peak response of the ▲corresponding▲ (IRA 1-Aug-2024) norgestimate isomer from the *Standard solution*

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

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

P = fraction of (*E*)- or (*Z*)-norgestimate in USP Norgestimate RS

Calculate the ratio of U_E to U_Z:

▲$$\text{Result} = (U_E/U_Z)$$

U_E = percentage of (*E*)-norgestimate in the *Sample solution* (%)

U_Z = percentage of (*Z*)-norgestimate in the *Sample solution* (%)

▲ (IRA 1-Aug-2024)

Acceptance criteria

Content: 98.0%–102.0% on the dried basis

Ratio of (*E*)- to (*Z*)-isomer: 1.27–1.78

IMPURITIES

• **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.3%

Change to read:

• **ORGANIC IMPURITIES, PROCEDURE 1**

Diluent, Mobile phase, ▲▲ (IRA 1-Aug-2024) and **Sample solution:** Prepare as directed in the *Assay*.

System suitability solution: 0.5 mg/mL each of USP Norgestimate RS, USP Norgestimate Related Compound A RS, and ▲USP Norelgestromin RS▲ (IRA 1-Aug-2024) in *Diluent*

▲**Sensitivity solution:** 0.4 µg/mL of USP Norgestimate RS in *Diluent*

Standard solution: 0.0008 mg/mL of USP Norgestimate RS in *Diluent*▲ (IRA 1-Aug-2024)

Chromatographic system

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

Mode: LC

Detector: UV 244 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 25 µL

▲**Run time:** NLT 1.5 times the retention time of (*E*)-norgestimate▲ (IRA 1-Aug-2024)

System suitability

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

[NOTE—The relative retention times in *Table 1* are provided as information that could aid in peak assignment.]

Table 1▲ (IRA 1-Aug-2024)

Name	Relative Retention Time
▲(*Z*)-Norelgestromin▲ (IRA 1-Aug-2024)	0.50
▲(*E*)-Norelgestromin▲ (IRA 1-Aug-2024)	0.56
Norgestimate related compound A▲▲ (IRA 1-Aug-2024)	0.72
(*Z*)-Norgestimate	0.86
(*E*)-Norgestimate	1.0

Suitability requirements

Resolution: NLT 1.5 between ▲(*Z*)-norelgestromin and (*E*)-norelgestromin;▲ (IRA 1-Aug-2024) NLT 1.5 between ▲(*E*)-norelgestromin▲ (IRA 1-Aug-2024) and norgestimate related compound A, *System suitability solution*

Tailing factor: NMT 1.5 for (*E*)-norgestimate and (*Z*)-norgestimate, *System suitability solution*

Relative standard deviation: ▲NMT 5.0% for (*E*)-norgestimate, *Standard solution*▲ (IRA 1-Aug-2024)

Signal-to-noise ratio: NLT ▲10▲ (IRA 1-Aug-2024) for ▲(*E*)▲ (IRA 1-Aug-2024) -norgestimate, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ▲any▲ (IRA 1-Aug-2024) impurity in the portion of Norgestimate taken:

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

r_U = peak ▲response▲ (IRA 1-Aug-2024) of each impurity from the *Sample solution*

r_S = peak ▲response▲ (IRA 1-Aug-2024) of (*E*)-norgestimate from the *Standard solution*

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

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

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

P = fraction of (*E*)-norgestimate in USP Norgestimate RS

Acceptance criteria: See *Table 2*. ▲The reporting threshold is 0.05%.▲ (IRA 1-Aug-2024)

Table 2

Name	Relative Response Factor	Acceptance Criteria, NMT (%)
▲(*Z*)-Norelgestromin▲ (IRA 1-Aug-2024) [a]	0.83	0.3
▲(*E*)-Norelgestromin▲ (IRA 1-Aug-2024) [a]	1.13	0.3
Norgestimate related compound A▲▲ (IRA 1-Aug-2024)	0.85	0.3
▲▲ (IRA 1-Aug-2024)	▲▲ (IRA 1-Aug-2024)	▲▲ (IRA 1-Aug-2024)
▲▲ (IRA 1-Aug-2024)	▲▲ (IRA 1-Aug-2024)	▲▲ (IRA 1-Aug-2024)
Any ▲unspecified▲ (IRA 1-Aug-2024) impurity	1.0	0.1

[a] The combined limits for (*Z*)- and (*E*)- ▲norelgestromin.▲ (IRA 1-Aug-2024)

Change to read:

• **Organic Impurities, Procedure 2**

Mobile phase: Cyclohexane and absolute alcohol (50:1)

Sensitivity solution: 0.5 µg/mL of USP Norgestimate RS in *Mobile phase*▲▲ (IRA 1-Aug-2024)

Standard solution: 1.0 mg/mL of USP Norgestimate RS in *Mobile phase*

Sample solution: 1.0 mg/mL of Norgestimate in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L20

Flow rate: 1 mL/min

Injection volume: 25 µL

▲**Run time:** NLT 1.6 times the retention time of (*E*)-norgestimate▲ (IRA 1-Aug-2024)

System suitability

Samples: *Sensitivity solution* and *Standard solution*

[Note— ▲The relative retention times in *Table 3* are provided as information that could aid in peak assignment.▲ (IRA 1-Aug-2024)]

▲**Table 3**▲ (IRA 1-Aug-2024)

Name	Relative Retention Time
▲(*Z*)-Norgestimate 5(10)-ene analog[a]▲ (IRA 1-Aug-2024)	0.74
▲(*E*)-Norgestimate 5(10)-ene analog[b]▲ (IRA 1-Aug-2024)	0.78
▲Norgestimate 5-ene analog[c]▲ (IRA 1-Aug-2024)	0.91

Name	Relative Retention Time
(*E*)-Norgestimate	1.0
(*Z*)-Norgestimate	1.1

[a] (*Z*)-13-Ethyl-17β-acetoxy-18,19-dinor-17α-pregn-5(10)-en-20-yn-3-one oxime.

[b] (*E*)-13-Ethyl-17β-acetoxy-18,19-dinor-17α-pregn-5(10)-en-20-yn-3-one oxime.

[c] Mixture of (*E*) and (*Z*)-13-Ethyl-17β-acetoxy-18,19-dinor-17α-pregn-5-en-20-yn-3-one oxime.

Suitability requirements

Resolution: NLT 1.5 between (*Z*)-norgestimate and (*E*)-norgestimate, *Standard solution*

Tailing factor: NMT 1.5 ▲for (*Z*)-norgestimate and (*E*)-norgestimate,▲ (IRA 1-Aug-2024) *Standard solution*

Relative standard deviation: NMT 2.0% for the peak area ratio of (*Z*)-norgestimate to (*E*)-norgestimate, *Standard solution*

Signal-to-noise ratio: NLT 3.0 for (*E*)-norgestimate, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ▲any▲ (IRA 1-Aug-2024) impurity in the portion of Norgestimate taken:

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

r_U = peak ▲response▲ (IRA 1-Aug-2024) of each impurity from the *Sample solution*

r_S = peak ▲response▲ (IRA 1-Aug-2024) of (*E*)-norgestimate from the *Standard solution*

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

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

F = relative response factor for each impurity (see *Table 4*)

P = fraction of (*E*)-norgestimate in USP Norgestimate RS

Acceptance criteria: See *Table 4*.

Table 4

Name	Relative Response Factor	Acceptance Criteria, NMT (%)
▲(*Z*)-Norgestimate 5(10)-ene analog▲ (IRA 1-Aug-2024)	1.4	0.2
▲(*E*)-Norgestimate 5(10)-ene analog▲ (IRA 1-Aug-2024)	1.5	0.1
▲Norgestimate 5-ene analog▲ (IRA 1-Aug-2024)	1.2	0.1
▲▲ (IRA 1-Aug-2024)	▲▲ (IRA 1-Aug-2024)	▲▲ (IRA 1-Aug-2024)
▲▲ (IRA 1-Aug-2024)	▲▲ (IRA 1-Aug-2024)	▲▲ (IRA 1-Aug-2024)

Name	Relative Response Factor	Acceptance Criteria, NMT (%)
Total impurities[a]	—	1.0

[a] Sum of the impurities found in *Organic Impurities, Procedure 1* and *Organic Impurities, Procedure 2*.

Change to read:

• **▲Limit of Diisopropyl Ether▲** (IRA 1-Aug-2024)

Internal standard solution: ▲0.02 µL/mL▲ (IRA 1-Aug-2024) of isobutyl alcohol in dimethylformamide

▲Sensitivity solution: 0.0005 µL/mL of diisopropyl ether in *Internal standard solution*▲ (IRA 1-Aug-2024)

Standard solution: ▲0.05 µL/mL of diisopropyl ether▲ (IRA 1-Aug-2024) in *Internal standard solution* ▲▲ (IRA 1-Aug-2024)

Sample solution: ▲20 mg/mL of Norgestimate in *Internal standard solution*.▲ (IRA 1-Aug-2024) Shake ▲▲ (IRA 1-Aug-2024) to dissolve.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 30-m▲; 1-µm coating of▲ (IRA 1-Aug-2024) phase G16

Temperatures

Injection port: 180°

Detector: 250°

Column: See *Table 5*.

Table 5

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
65	▲0▲ (IRA 1-Aug-2024)	65	2.5
65	35	100	2
100	30	160	2.5

Carrier gas: Helium

Flow rate: 6 mL/min

Injection mode: Split

Split flow: 16 mL/min

Injection volume: 1 µL

System suitability

Samples: *Internal standard solution*, ▲*Sensitivity solution*,▲ (IRA 1-Aug-2024) and *Standard solution*

[Note— ▲The relative retention times for diisopropyl ether and the isobutyl alcohol internal standard are 1.0 and 2.4, respectively.▲ (IRA 1-Aug-2024)]

Suitability requirements

▲Blank interference:▲ (IRA 1-Aug-2024) There are no interfering peaks due to dimethylformamide▲, *Internal standard solution*.▲ (IRA 1-Aug-2024)

Relative standard deviation: NMT 3.0%, determined from the peak response ratio of ▲diisopropyl ether▲ (IRA 1-Aug-2024) to the internal standard, *Standard solution*

Signal-to-noise ratio: NLT 2.0 for ▲diisopropyl ether, *Sensitivity solution*▲ (IRA 1-Aug-2024)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ▲diisopropyl ether▲ (IRA 1-Aug-2024) in the portion of Norgestimate taken:

$$\text{Result} = {}^{\blacktriangle}(R_U/R_S) \times (C_S/C_U) \times F \times D \times 100{}^{\blacktriangle}\ \text{(IRA 1-Aug-2024)}$$

R_U = peak response ratio of ▲diisopropyl ether▲ (IRA 1-Aug-2024) to the internal standard from the *Sample solution*

R_S = peak response ratio of ▲diisopropyl ether▲ (IRA 1-Aug-2024) to the internal standard from the *Standard solution*

C_S = concentration of ▲diisopropyl ether▲ (IRA 1-Aug-2024) in the *Standard solution* (▲µL▲ (IRA 1-Aug-2024) /mL)

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

F = conversion factor, 0.001 mL/µL▲ (IRA 1-Aug-2024)

D = density of ▲diisopropyl ether▲ (IRA 1-Aug-2024) (mg/mL)

▲▲ (IRA 1-Aug-2024)

Acceptance criteria: ▲▲ (IRA 1-Aug-2024) NMT 0.05%

▲▲ (IRA 1-Aug-2024)

SPECIFIC TESTS

Change to read:

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

Sample solution: 10 mg/mL in ▲methylene chloride▲ (IRA 1-Aug-2024)

Acceptance criteria: ▲+42.0° to +50.0°, determined at 20°▲ (IRA 1-Aug-2024)

• **Loss on Drying** ⟨731⟩

Analysis: Dry at 105° for 3 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers.

Change to read:

• **USP Reference Standards** ⟨11⟩

▲USP Norelgestromin RS▲ (IRA 1-Aug-2024)

USP Norgestimate RS

USP Norgestimate Related Compound A RS

▲13-Ethyl-18,19-dinor-17α-pregn-4-en-20-yn-3-oxo-17β-yl acetate;
Also known as▲ (IRA 1-Aug-2024) levonorgestrel acetate.

$C_{23}H_{30}O_3$ ▲354.49▲ (IRA 1-Aug-2024)

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

Topic/Question	Contact	Expert Committee
NORGESTIMATE	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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