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Etomidate Injection

DEFINITION

Etomidate Injection is a sterile, nonpyrogenic solution. It contains NLT 90.0% and NMT 110.0% of the labeled amount of etomidate ($C_{14}H_{16}N_2O_2$). It may contain suitable buffers and preservatives.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*: 197U**▲ (CN 1-May-2020)

Sample solution: 10 µg/mL of etomidate in isopropyl alcohol

Medium: Isopropyl alcohol

Acceptance criteria: Meets the requirements

• **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: 0.7 g/L of monobasic sodium phosphate in water

Mobile phase: Acetonitrile and *Buffer* (2:3)

Standard solution: 0.16 mg/mL of USP Etomidate RS in acetonitrile

Sample solution: Nominally 0.16 mg/mL of etomidate from Injection in acetonitrile

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 30-cm; packing L1

Flow rate: 2.3 mL/min

Injection volume: 20 µL

Run time: NLT 3 times the retention time of etomidate

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of etomidate ($C_{14}H_{16}N_2O_2$) in the portion of Injection 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 Etomidate RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

IMPURITIES

• **Organic Impurities, Procedure 1: Related Compounds**

Solution A: Dissolve 6 g of sodium citrate dihydrate and 4 g of anhydrous citric acid in 1 L of water.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
20	30	70
21	95	5
30	95	5

Diluent: Weigh 6 g of sodium citrate dihydrate and 4 g of anhydrous citric acid into a 1000-mL volumetric flask. Add 500 mL of water, and shake to dissolve. Add 110 mL of acetonitrile and 50 mL of methanol, and dilute with water to volume.

System suitability solution: 0.02 mg/mL each of USP Etomidate RS and USP Metomidate Hydrochloride RS in *Diluent*

Standard stock solution: 0.1 mg/mL of USP Metomidate Hydrochloride RS in methanol

Standard solution: 0.004 mg/mL of USP Metomidate Hydrochloride RS from the *Standard stock solution* in *Diluent*

Sensitivity solution: 0.8 µg/mL of USP Metomidate Hydrochloride RS from the *Standard solution* in *Diluent*

Sample solution: Nominally 0.8 mg/mL of etomidate from Injection in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 30-cm; packing L1

Flow rate: 2.0 mL/min

Injection volume: 50 µL

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between etomidate and metomidate, *System suitability solution*

Relative standard deviation: NMT 3.0%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

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

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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

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

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

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

M_{r1} = molecular weight of metomidate free base, 230.26

M_{r2} = molecular weight of metomidate hydrochloride, 266.72

Acceptance criteria: See *Table 2*. [NOTE—Disregard any impurity peaks less than 0.05%.]

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Etomidate acid[a]	0.34	1.4
Propylene glycol ester[b]	0.77	—

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Metomidate[c]	0.90	0.1
Etomidate	1.0	—
Any unspecified impurity	—	0.1
Total impurities	—	1.6

[a] 1-(1-Phenylethyl)-1*H*-imidazole-5-carboxylic acid.

[b] This is quantitated in *Organic Impurities, Procedure 2: Total Propylene Glycol Esters*.

[c] Methyl 1-(1-phenylethyl)-1*H*-imidazole-5-carboxylate.

• **Organic Impurities, Procedure 2: Total Propylene Glycol Esters:** [Note—Perform this test if propylene glycol is used in the formulation.]

Mobile phase and **Chromatographic system:** Proceed as directed in the *Assay*.

Sensitivity solution: 1.6 µg/mL of USP Etomidate RS in acetonitrile

Standard solution: 0.025 mg/mL of USP Etomidate RS in acetonitrile

Sample solution: Nominally 1.6 mg/mL of etomidate from Injection in acetonitrile

System suitability

Samples: *Sensitivity solution* and *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 3.0%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

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

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

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

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

F = relative response factor for each individual impurity (see *Table 3*)

Acceptance criteria: See *Table 3*. Disregard any impurity peaks less than 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Etomidate acid[a]	0.16	—	—
Total propylene glycol esters[b]	0.40	0.9	2.8
Etomidate	1.0	1.0	—
Any unspecified impurity	—	1.0	0.1
Total impurities[c]	—	—	4.0

[a] This is quantitated in *Organic Impurities, Procedure 1: Related Compounds*.

[b] 2-Hydroxypropyl ester and 2-hydroxy-1-methylethyl ester.

[c] Total impurities include all impurities from *Table 2* and *Table 3*.

SPECIFIC TESTS

- **Bacterial Endotoxins Test ⟨85⟩:** It contains NMT 8.35 USP Endotoxin Units/mg of etomidate.
- **Sterility Tests ⟨71⟩, *Test for Sterility of the Product to Be Examined, Membrane Filtration*:** Meets the requirements
- **pH ⟨791⟩:** Between 4.0 and 7.0
- **Particulate Matter in Injections ⟨788⟩:** It meets the requirements for small-volume injections.
- **Other Requirements:** It meets the requirements in *Injections and Implanted Drug Products ⟨1⟩*.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in single-dose containers. Store at controlled room temperature.
- **USP Reference Standards ⟨11⟩**

USP Etomidate RS

USP Metomidate Hydrochloride RS

Methyl 1-(1-phenylethyl)-1*H*-imidazole-5-carboxylate hydrochloride.

$C_{13}H_{14}N_2O_2 \cdot HCl$ 266.72

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

Topic/Question	Contact	Expert Committee
ETOMIDATE INJECTION	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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