Miconazole Nitrate

Type of Posting	Revision Bulletin
Posting Date	26–Apr–2019
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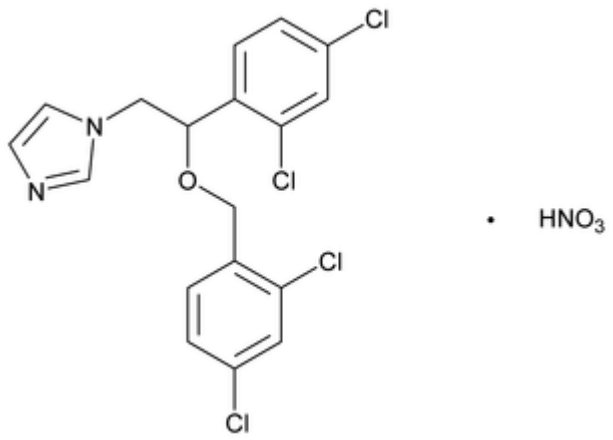
Expert Committee	Chemical Medicines Monographs 6
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 6 Expert Committee has revised the Miconazole Nitrate monograph. The purpose for the revision is to revise the test for *Optical Rotation <781S>, Procedures, Specific Rotation* to *Optical Rotation <781A>, Procedures*, *Angular Rotation* measured at 20°. The revision will accommodate products in the market.

The Miconazole Nitrate Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Richard Nguyen, Scientific Liaison to the Chemical Medicines Monographs 6 Expert Committee at (301-816-8170 or rbn@usp.org).

Miconazole Nitrate



$C_{18}H_{14}Cl_4N_2O \cdot HNO_3$ 479.14

1*H*-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-, mononitrate;
1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl] imidazole mononitrate [22832-87-7].

DEFINITION

Miconazole Nitrate contains NLT 98.0% and NMT 102.0% of miconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$), calculated on the dried basis.

IDENTIFICATION

- **A. Infrared Absorption** ⟨197⟩**:** [Note—Methods described in ⟨197K⟩ or ⟨197A⟩ may be used.]
- **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: Methanol, water, and 1 M triethylammonium acetate (30:70:1)
Solution B: Acetonitrile, methanol, and 1 M triethylammonium acetate (25: 75: 0.2)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	70	30
5	70	30
10	44	56
27	44	56
30	25	75
35	25	75
36	70	30
40	70	30

Diluent: Methanol and water (70:30)
System suitability solution: 0.1 mg/mL of USP Miconazole Nitrate RS and 6 µg/mL of USP Miconazole Related Compound F RS in *Diluent*. Sonication may be needed to aid dissolution.
Standard solution: 0.1 mg/mL of USP Miconazole Nitrate RS in *Diluent*. Sonication may be needed to aid dissolution.
Sample solution: 0.1 mg/mL of Miconazole Nitrate in *Diluent*. Sonication may be needed to aid dissolution.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 215 nm
Column: 4.6-mm × 10-cm; 2.6-µm packing L11
Column temperature: 40°
Flow rate: 0.8 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[Note—The relative retention times for miconazole related compound F and miconazole are 0.96 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 1.5 between miconazole related compound F and miconazole, *System suitability solution*
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 0.73%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of miconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$) in the portion of Miconazole Nitrate taken:

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

r_U = peak response of miconazole from the *Sample solution*
r_S = peak response of miconazole from the *Standard solution*
C_S = concentration of USP Miconazole Nitrate RS in the *Standard solution* (mg/mL)
C_U = concentration of Miconazole Nitrate in the *Sample solution* (mg/mL)

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

IMPURITIES

- **Residue on Ignition** ⟨281⟩**:** NMT 0.2%
- **Organic Impurities**

Solution A, Solution B, Mobile phase, Diluent, and **Chromatographic system:** Proceed as directed in the *Assay*.
Standard solution: 1.2 µg/mL each of USP Miconazole Nitrate RS, USP Econazole Nitrate RS, USP Miconazole Related Compound C RS, USP Miconazole Related Compound F RS, and USP Miconazole Related Compound I RS in *Diluent*
Sample solution: 600 µg/mL of Miconazole Nitrate in *Diluent*. Sonication may be needed to aid dissolution.
System suitability
Sample: *Standard solution*
[Note—See *Table 2* for relative retention times.]
Suitability requirements
Resolution: NLT 1.5 between miconazole related compound C and miconazole related compound I; NLT 1.5 between miconazole related compound I and econazole; and NLT 1.5 between miconazole related compound F and miconazole
Relative standard deviation: NMT 3.0% for miconazole
Analysis
Samples: *Standard solution* and *Sample solution*

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Calculate the percentage of miconazole related compound C, miconazole related compound F, miconazole related compound I, or econazole nitrate in the portion of Miconazole Nitrate taken:

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

r_U = peak response of miconazole related compound C, miconazole related compound F, miconazole related compound I, or econazole nitrate from the *Sample solution*
r_S = peak response of miconazole related compound C, miconazole related compound F, miconazole related compound I, or econazole nitrate from the *Standard solution*
C_S = concentration of USP Miconazole Related Compound C RS, USP Miconazole Related Compound F RS, USP Miconazole Related Compound I RS, or USP Econazole Nitrate RS in the *Standard solution* (µg/mL)
C_U = concentration of Miconazole Nitrate in the *Sample solution* (µg/mL)

Calculate the percentage of each specified and any individual unspecified impurity in the portion of Miconazole Nitrate taken:

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

r_U = peak response of each specified and any individual unspecified impurity from the *Sample solution*
r_S = peak response of miconazole from the *Standard solution*
C_S = concentration of USP Miconazole Nitrate RS in the *Standard solution* (µg/mL)
C_U = concentration of Miconazole Nitrate in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Deschlorobenzyl econazole[a]	0.22	0.25
Miconazole quarternary salt[b]	0.57	0.25
Miconazole benzyl analog[c]	0.65	0.25
Miconazole related compound C	0.74	0.25
Miconazole related compound I	0.76	0.25
Econazole nitrate	0.78	0.25
Miconazole 2,6-isomer[d]	0.87	0.25
Miconazole 2,5-isomer[e]	0.94	0.25
Miconazole related compound F	0.96	0.25
Miconazole	1.0	—
Any individual unspecified impurity	—	0.10
Total impurities	—	0.5

[a] 1-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol.
[b] 2-(3-{2-[(2,4-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl}-1*H*-imidazol-3-ium-1-yl)-2-methylpropanoate.
[c] 1-[2-(Benzyloxy)-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole.
[d] 1-{2-[(2,6-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl}-1*H*-imidazole.
[e] 1-{2-[(2,5-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl}-1*H*-imidazole.

SPECIFIC TESTS

Change to read:

- **▲Optical Rotation** ⟨781A⟩**,** *Procedures, Angular Rotation*▲ (RB 1-May-2019)
  Sample solution: 10 mg/mL of Miconazole Nitrate in methanol
  Acceptance criteria: –0.10° to +0.10° ▲at 20°▲ (RB 1-May-2019)
- **Loss on Drying** ⟨731⟩
  Analysis: Dry at 105° for 2 h.
  Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers, protected from light. Store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩
  USP Econazole Nitrate RS
  USP Miconazole Nitrate RS
  USP Miconazole Related Compound C RS
  2-[(2,4-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl) ethan-1-amine hydrochloride.
  $C_{15}H_{13}Cl_4NO \cdot HCl$ 401.53
  USP Miconazole Related Compound F RS
  1-{2-[(3,4-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl) ethyl}-1*H*-imidazole.
  $C_{18}H_{14}Cl_4N_2O$ 416.13
  USP Miconazole Related Compound I RS
  1-{2-[(2-Chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl} -1*H*-imidazole mononitrate.
  $C_{18}H_{15}Cl_3N_2O \cdot HNO_3$ 444.69

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