Metronidazole Gel

Type of Posting	Notice of Intent to Revise
Posting Date	26–May–2017
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 1

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the USP Chemical Medicines Monographs 1 Expert Committee intends to revise the Metronidazole Gel monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the pH limit in the monograph from 4.0–6.5 to 4.0–6.8.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Shankari Shivaprasad**,** Ph.D., Senior Scientific Liaison to the Chemical Medicines Monographs 1 Expert Committee (301–230–7426 or sns@usp.org).

[1] This text is not the official version of a USP–NF monograph and may not reflect the full and accurate contents of the monograph in effect today. Please refer to the current edition of the USP–NF for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this pending monograph receives FDA approval. Once FDA approval is granted, the official monograph will include the changes indicated herein and any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval.

Metronidazole Gel

DEFINITION

Metronidazole Gel contains NLT 90.0% and NMT 110.0% of the labeled amount of metronidazole ($C_6H_9N_3O_3$).

IDENTIFICATION

- **A.** The UV spectrum of the metronidazole peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **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 and water (20:80)
Solution B: Methanol
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
10.0	100	0
15.0	10	90
15.1	100	0
20.0	100	0

System suitability solution: 0.6 µg/mL of USP Metronidazole RS and 0.6 µg/mL of USP Tinidazole Related Compound A RS in *Solution A*
Standard solution: 30 µg/mL of USP Metronidazole RS in *Solution A*
Sample stock solution: Nominally 300 µg/mL of metronidazole in *Solution A* prepared as follows. Transfer a portion of Gel to a suitable volumetric flask. Add *Solution A* equivalent to 50% of the flask volume and sonicate or vortex until dissolved. Dilute with *Solution A* to volume. [NOTE—On the basis of formulation, if necessary, centrifuge a portion of the solution at 3000 rpm for 10 min and pass a portion of the supernatant through a filter of 0.45-µm pore size. Use the filtrate.]
Sample solution: Nominally 30 µg/mL of metronidazole in *Solution A* prepared from the *Sample stock solution*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 319 nm. For *Identification A*, use a diode array detector in the range of 210–500 nm.
Column: 4.6-mm × 15-cm; 5-µm packing L7
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 30 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—See *Table 2* for the relative retention times.]
Suitability requirements
Resolution: NLT 2.0 between metronidazole and tinidazole related compound A, *System suitability solution*
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of metronidazole ($C_6H_9N_3O_3$) in the portion of Gel taken:

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

r_U = peak response of metronidazole from the *Sample solution*
r_S = peak response of metronidazole from the *Standard solution*
C_S = concentration of USP Metronidazole RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of metronidazole in the *Sample solution* (µg/mL)
Acceptance criteria: 90.0%–110.0%

IMPURITIES

- **ORGANIC IMPURITIES**

Solution A, Solution B, Mobile phase, and **Chromatographic system:** Proceed as directed in the *Assay*.
Standard solution: Use the *System suitability solution* from the *Assay*.
Sample solution: Use the *Sample stock solution* from the *Assay*.
System suitability
Sample: *Standard solution*
[NOTE—See *Table 2* for the relative retention times.]
Suitability requirements
Resolution: NLT 2.0 between metronidazole and tinidazole related compound A
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of tinidazole related compound A in the portion of Gel taken:

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

r_U = peak response of tinidazole related compound A from the *Sample solution*
r_S = peak response of tinidazole related compound A from the *Standard solution*
C_S = concentration of USP Tinidazole Related Compound A RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of metronidazole in the *Sample solution* (µg/mL)
Calculate the percentage of each individual unspecified impurity in the portion of Gel taken:

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

r_U = peak response of each unspecified impurity from the *Sample solution*
r_S = peak response of metronidazole from the *Standard solution*
C_S = concentration of USP Metronidazole RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of metronidazole in the *Sample solution* (µg/mL)
Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Tinidazole related compound A	0.76	0.2
Metronidazole	1.0	—

Table 2 *(Continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Any individual unspecified impurity	—	0.3
Total impurities	—	1.0

PERFORMANCE TESTS

• **MINIMUM FILL** ⟨**755**⟩**:** Meets the requirements

SPECIFIC TESTS

Change to read:

• **PH** ⟨**791**⟩**:** The apparent pH determined potentiometrically is between ►4.0 and 6.8.◄ (TBD)

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in laminated collapsible tubes at controlled room temperature.

• **USP REFERENCE STANDARDS** ⟨**11**⟩

USP Metronidazole RS

USP Tinidazole Related Compound A RS

2-Methyl-5-nitroimidazole.

$C_4H_5N_3O_2$ 127.10