Dextromethorphan

Type of Posting	Revision Bulletin
Posting Date	27–May–2016, updated 30–Dec–2016[1]
Target Official Date	01–Mar–2017
Expert Committee	Chemical Medicines Monographs 6
Reason for Revision	Safety

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 6 Expert Committee has revised the Dextromethorphan monograph.

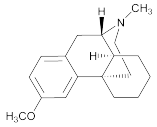
The purpose of this revision is to introduce a procedure to quantitatively monitor the presence of levomethorphan in Dextromethorphan.

The Dextromethorphan Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated into *USP 40–NF 35*.

Should you have questions, please contact Clydewyn M. Anthony, Ph. D, Senior Scientific Liaison (301-816-8139 or cma@usp.org).

[1] The official date for the Dextromethorphan Revision Bulletin was changed from January 1, 2017 to March 1, 2017 on December 30, 2016.

Dextromethorphan



$C_{18}H_{25}NO$ 271.40
Morphinan, 3-methoxy-17-methyl-, (9α,13α,14α)-;
3-Methoxy-17-methyl-9α,13α,14α-morphinan [125-71-3].

DEFINITION

Dextromethorphan contains NLT 98.0% and NMT 101.0% of dextromethorphan ($C_{18}H_{25}NO$), calculated on the anhydrous basis.

IDENTIFICATION

• **A. Infrared Absorption** ⟨197K⟩

Delete the following:

•• **B. Ultraviolet Absorption** ⟨197U⟩
Analytical wavelength: 278 nm
Sample solution: 100 µg/mL in dilute hydrochloric acid (1 in 120)
Acceptance criteria: Absorptivities, calculated on the anhydrous basis, do not differ by more than 3.0%.● (RB 1-Mar-2017)

Add the following:

•• **B.**
Buffer: 1.54 g of ammonium acetate in 1 L of water, adjusted with phosphoric acid to a pH of 4.1
Mobile phase: Methanol and *Buffer* (90:10)
Diluent: Methanol and water (90:10)
System suitability solution: 10 µg/mL of levomethorphan from USP Levomethorphan Solution RS and 10 mg/mL of USP Dextromethorphan RS in *Diluent*
Standard solution: 10 µg/mL of USP Dextromethorphan RS in *Diluent*
Sample solution: 10.0 mg/mL of Dextromethorphan in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: 225 nm
Column: 4.6-mm × 25-cm; 5-µm packing L88
Flow rate: 1 mL/min
Injection volume: 4 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for dextromethorphan and levomethorphan are 1.0 and 1.28, respectively.]
Suitability requirements
Resolution: NLT 2.0 between dextromethorphan and levomethorphan, *System suitability solution*
Relative standard deviation: NMT 5.0% for dextromethorphan, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of levomethorphan in the portion of Dextromethorphan taken:

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

r_U = peak response of levomethorphan from the *Sample solution*
r_S = peak response of dextromethorphan from the *Standard solution*
C_S = concentration of USP Dextromethorphan RS in the *Standard solution* (mg/mL)
C_U = concentration of Dextromethorphan in the *Sample solution* (mg/mL)
Acceptance criteria: NMT 0.10%● (RB 1-Mar-2017)

ASSAY

• **Procedure**
Sample solution: Dissolve 700 mg of Dextromethorphan in 60 mL of glacial acetic acid, warming slightly, if necessary, to dissolve.
Titrimetric system
Mode: Direct titration
Titrant: 0.1 N perchloric acid VS
Endpoint detection: Visual
Analysis: Add 2 drops of crystal violet TS to the *Sample solution* and titrate with *Titrant* to a blue-green endpoint. Perform a blank determination and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 27.14 mg of dextromethorphan ($C_{18}H_{25}NO$).
Acceptance criteria: 98.0%–101.0% on the anhydrous basis

IMPURITIES

• **Residue on Ignition** ⟨281⟩**:** NMT 0.1%

Delete the following:

•• **Heavy Metals** ⟨231⟩**,** *Method II***:** NMT 20 ppm

● (Official 1-Jan-2018)

• **Limit of Phenolic Compounds**
Sample: 10 mg of Dextromethorphan
Analysis: Dissolve the *Sample* in 2 mL of 3 N hydrochloric acid, add 2 drops of ferric chloride TS, and mix. Add 2 drops of potassium ferricyanide TS, and observe after 2 min.
Acceptance criteria: No blue-green color develops.

• **Limit of *N,N*-Dimethylaniline**
Standard solution: Transfer 50 mg of *N,N*-dimethylaniline to a 100-mL volumetric flask, add 70.0 mL of water, insert the stopper tightly, shake for 20 min using a mechanical wrist-action shaker or equivalent, and dilute with water to volume. Transfer 1.0 mL to a 100-mL volumetric flask, and dilute with water to volume. Transfer 1.0 mL of the resulting solution to a 25-mL volumetric flask, and add 19 mL of water.
Sample solution: Transfer 500 mg of Dextromethorphan to a 25-mL volumetric flask, add 19 mL of water and 1 mL of 3 N hydrochloric acid, dissolve by warming on a steam bath, and cool.
Analysis: Add 2 mL of 1 N acetic acid and 1 mL of sodium nitrite solution (1 in 100) to the *Sample solution* and dilute with water to volume. This solution shows no more color than the straw yellow to greenish yellow color of the *Standard solution* similarly treated.
Acceptance criteria: NMT 0.001% of *N,N*-dimethylaniline

SPECIFIC TESTS

Delete the following:

•• **MELTING RANGE OR TEMPERATURE** ⟨**741**⟩**,** *Procedures, Class I***:** 109.5°–112.5°● (RB 1-Mar-2017)

Delete the following:

•• **OPTICAL ROTATION** ⟨**781S**⟩**,** *Procedures, Specific Rotation*
Standard solution: 100 mg/mL USP Dextromethorphan RS in chloroform
Sample solution: 100 mg/mL of Dextromethorphan in chloroform
Acceptance criteria: The specific rotation of the *Sample solution* does not differ from that of the *Standard solution* by more than 1.0%.● (RB 1-Mar-2017)

• **WATER DETERMINATION** ⟨**921**⟩**,** *Method I, Method Ia***:** NMT 0.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers.

Change to read:

• **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Dextromethorphan RS
•USP Levomethorphan Solution RS
3-Methoxy-17-methylmorphinan.
$C_{18}H_{25}NO$ 271.40
This solution contains 0.1 mg/mL of levomethorphan in methanol.● (RB 1-Mar-2017)