Moxidectin

Type of Posting	Notice of Intent to Revise
Posting Date	27–Apr–2018
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 3

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 3 Expert Committee intends to revise the Moxidectin monograph.

Based on supporting documents received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Labeling statement in the monograph for Moxidectin to allow flexibility for indications where products using the drug substance are intended for human use.

The proposed revision is contingent on FDA approval of a product intended for use in humans. 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.

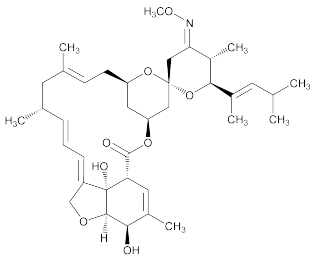
See below for additional information about the proposed text.[1]

Should you have any questions, please contact Morgan Puderbaugh, Senior Scientific Liaison to the Chemical Medicines Monographs 3 Expert Committee (301-998-6833 or mxp@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 currently official monograph. 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 proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted which will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program which are posted without prior publication for comment in *Pharmacopeial Forum*, must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP-NF* for Revision Bulletins.

Moxidectin



$C_{37}H_{53}NO_8$ 639.82

(6*R*,25*S*)-5-*O*-Demethyl-28-deoxy-25-[(*E*)-1,3-dimethyl-1-butenyl]-6,28-epoxy-23-oxomilbemycin B 23-(*E*)-(*O*-methyloxime);

(2a*E*,4*E*,5′*R*,6*R*,6′*S*,8*E*,11*R*,13*S*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6′-[(*E*)-1,3-Dimethyl-1-butenyl]-5′,6,6′,7,10,11,14,15,17a,20,20a,20b-dodecahydro-20,20b-dihydroxy-5′,6,8,19-tetramethylspiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-4′,17(3′*H*)-dione 4′-(*E*)-(*O*-methyloxime) [113507-06-5].

DEFINITION

Moxidectin contains NLT 92.0% and NMT 102.0% of moxidectin ($C_{37}H_{53}NO_8$), calculated on the anhydrous basis. It may contain a suitable antioxidant.

IDENTIFICATION

- **A. Infrared Absorption ⟨197K⟩**
- **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: Dissolve 7.7 g of ammonium acetate in 400 mL of water, and adjust with glacial acetic acid to a pH of 4.8.

Mobile phase: Acetonitrile and *Buffer* (60:40)

Standard solution: 1.0 mg/mL of USP Moxidectin RS in acetonitrile. Sonicate if necessary to facilitate dissolution.

Sample solution: 1.0 mg/mL of Moxidectin in acetonitrile. Sonicate if necessary to facilitate dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 242 nm

Column: 3.9-mm × 15-cm; 4-µm packing L1

Column temperature: 50°

Flow rate: 2.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 1%, for 4 replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of moxidectin ($C_{37}H_{53}NO_8$) in the portion of Moxidectin 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 Moxidectin RS in the *Standard solution* (mg/mL)
C_U = concentration of Moxidectin in the *Sample solution* (mg/mL)

Acceptance criteria: 92.0%–102.0% on the anhydrous basis

IMPURITIES

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

Delete the following:

▲ • **Heavy Metals,** *Method II* **⟨231⟩:** NMT 20 ppm ▲ (Official 1-Jan-2018)

- **Organic Impurities: Early-Eluting Impurities**

Buffer, Mobile phase, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability solution: 1.0 mg/mL of USP Moxidectin System Suitability Mixture RS in acetonitrile. Sonicate if necessary to facilitate dissolution.

Standard solution: 0.01 mg/mL of Moxidectin in acetonitrile from the *Sample solution*

System suitability

Sample: *System suitability solution*

Suitability requirements

Peak-to-valley ratio: NLT 3.0 between moxidectin 17a-epimer and moxidectin

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each early-eluting impurity in the portion of Moxidectin taken:

$$\text{Result} = (r_U/r_S) \times F \times D \times 100$$

r_U = peak response of each early-eluting impurity from the *Sample solution*
r_S = peak response of moxidectin from the *Standard solution*
F = *Assay* value expressed as a decimal
D = dilution factor used to prepare the *Standard solution*, 0.01

Acceptance criteria: See *Table 1*. The reporting level for impurities is 0.1%. Disregard the peak due to the stabilizer (identify this peak, where applicable, by injecting a suitable reference solution).

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Moxidectin butenyl analog[a]	0.5	1.5
5′-Demethyl moxidectin[b]	0.7	0.5
Moxidectin pentenyl analog[c]	0.75	1.5
Moxidectin 17a-epimer[d]	0.9	2.5
Moxidectin	1.0	—
Sum of moxidectin 19-*S*-17a-ene[e] and moxidectin ethyl isomers[f]	1.3–1.5	1.7[h]
Milbemycin B analog (moxidectin open ring)[g]	1.6	1.5

Table 1 *(continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Any other individual impurity eluting before milbemycin B analog (moxidectin open ring)	—	0.5

[a] (2a*E*,4*E*,5′*R*,6*R*,6′*S*,8*E*,11*R*,13*S*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6′-[(*E*)-But-2-en-2-yl]-5′,6,6′,7,10,11,14,15,17a,20,20a,20b-dodecahydro-20,20b-dihydroxy-5′,6,8,19-tetramethylspiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-4′,17(3′*H*)-dione 4′-(*E*)-(*O*-methyloxime).
[b] (2a*E*,4*E*,5′*R*,6*R*,6′*S*,8*E*,11*R*,13*S*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-5′,6,6′,7,10,11,14,15,17a,20,20a,20b-Dodecahydro-20,20b-dihydroxy-6′-[(*E*)-4-methylpent-2-en-2-yl]-6,8,19-trimethylspiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-4′,17(3′*H*)-dione 4′-(*E*)-(*O*-methyloxime).
[c] (2a*E*,4*E*,5′*R*,6*R*,6′*S*,8*E*,11*R*,13*S*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-5′,6,6′,7,10,11,14,15,17a,20,20a,20b-Dodecahydro-20,20b-dihydroxy-5′,6,8,19-tetramethyl-6′-[(*E*)-pent-2-en-2-yl]spiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-4′,17(3′*H*)-dione 4′-(*E*)-(*O*-methyloxime).
[d] (2a*E*,4*E*,5′*R*,6*R*,6′*S*,8*E*,11*R*,13*S*,15*S*,17a*S*,20*R*,20a*R*,20b*S*)-5′,6,6′,7,10,11,14,15,17a,20,20a,20b-Dodecahydro-20,20b-dihydroxy-6′-[(*E*)-4-methylpent-2-en-2-yl]-5′,6,8,19-tetramethylspiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-4′,17(3′*H*)-dione 4′-(*E*)-(*O*-methyloxime).
[e] (2a*E*,4*E*,5′*R*,6*R*,6′*S*,8*E*,11*R*,13*S*,15*S*,19*S*,20*R*,20a*R*,20b*S*)-5′,6,6′,7,10,11,14,15,19,20,20a,20b-Dodecahydro-20,20b-dihydroxy-6′-[(*E*)-4-methylpent-2-en-2-yl]-5′,6,8,19-tetramethylspiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-4′,17(3′*H*)-dione 4′-(*E*)-(*O*-methyloxime).
[f] Mixture of five possible isomers, where one methyl group in the analyte is replaced with an ethyl group.
[g] (2′*R*,3*S*,5′*S*,6′*S*,7*R*,9*E*,12*R*,13*E*,15*E*,16a*S*,18*S*,20a*R*)-16a,18-Dihydroxy-5′,10,12,16,19-pentamethyl-6′-[(*E*)-4-methylpent-2-en-2-yl]-3,4, 5′,6′,7,8,11,12,16a,17,18,20a-dodecahydro-1*H*-spiro[3,7-methanobenzo[*g*][1,5]dioxacyclooctadecin-5,2′-[2*H*]pyran]-14′-dione (*E*)-(*O*-methyloxime).
[h] If present, moxidectin 19-*S*-17a-ene and the moxidectin ethyl isomers may not be completely resolved by the method. These peaks are integrated together to determine conformance.

• ORGANIC IMPURITIES: LATE-ELUTING IMPURITIES

Buffer: Dissolve 3.8 g of ammonium acetate in 250 mL of water, and adjust with glacial acetic acid to a pH of 4.2.

Mobile phase: Acetonitrile and *Buffer* (75:25)

System suitability solution: 3.0 mg/mL of USP Moxidectin System Suitability Mixture RS in acetonitrile. Sonicate if necessary to facilitate dissolution.

Sample solution: 3.0 mg/mL of Moxidectin in acetonitrile. Sonicate if necessary to facilitate dissolution.

Standard solution: 0.03 mg/mL of Moxidectin in acetonitrile from the *Sample solution*

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 242 nm
Column: 3.9-mm × 15-cm; 4-µm packing L1
Column temperature: 35°
Flow rate: 2 mL/min
Injection volume: 10 µL
Run time: NLT 10 times the retention time of moxidectin

System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 1.0 between moxidectin deoxydiene/methylthiomethoxymoxidectin and 20b-methylthiomoxidectin

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each late-eluting impurity in the portion of Moxidectin taken:

$$\text{Result} = (r_U/r_S) \times F \times D \times 100$$

r_U = peak response of each late-eluting impurity from the *Sample solution*
r_S = peak response of moxidectin from the *Standard solution*
F = *Assay* value expressed as a decimal
D = dilution factor used to prepare the *Standard solution*, 0.01

Acceptance criteria: See *Table 2*. The reporting level for impurities is 0.1%. Disregard the peak due to the stabilizer (identify this peak, where applicable, by injecting a suitable reference solution).

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Moxidectin	1.0	—
Moxidectin deoxydiene[a] and 4′-methylthiomethoxymoxidectin[b]	2.0	1.0[e]
20b-Methylthiomoxidectin[c]	2.2	0.5
20-Nitrobenzoylmoxidectin[d]	3.4	0.5
Any other individual impurity eluting after the milbemycin B analog (moxidectin open ring) (≅1.4 RRT)	—	0.5

[a] (2a*E*,4*E*,5′*R*,6*R*,6′*S*,8*E*,11*R*,13*S*,15*S*,20a*R*,20b*S*)-5′,6,6′,7,10,11,14,15,20a,20b-Decahydro-20b-hydroxy-6′-[(*E*)-4-methylpent-2-en-2-yl]-5′,6,8,19-tetramethylspiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-4′,17(3′*H*)-dione 4′-(*E*)-(*O*-methyloxime).
[b] (2a*E*,4*E*,4′*S*,5′*R*,6*R*,6′*S*,8*E*,11*R*,13*S*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)- 3′,4′,5′,6,6′,7,10,11,14,15,17a,20,20a,20b-Tetradecahydro-20,20b-dihydroxy-6′-[(*E*)-4-methylpent-2-en-2-yl]-4′-methylthiomethoxy-5′,6,8,19-tetramethylspiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-17-one.
[c] (2a*E*,4*E*,5′*R*,6*R*,6′*S*,8*E*,11*R*,13*S*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-5′,6,6′,7,10,11,14,15,17a,20,20a,20b-Dodecahydro-20-hydroxy-6′-[(*E*)-4-methylpent-2-en-2-yl]-20b-methylthiomethoxy-5′,6,8,19-tetramethylspiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-4′,17(3′*H*)-dione 4′-(*E*)-(*O*-methyloxime).
[d] (2a*E*,4*E*,5′*R*,6*R*,6′*S*,8*E*,11*R*,13*S*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-5′,6,6′,7,10,11,14,15,17a,20,20a,20b-Dodecahydro-20b-hydroxy-6′-[(*E*)-4-methylpent-2-en-2-yl]-20-(4-nitrobenzoyloxy)-5′,6,8,19-tetramethylspiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-4′,17(3′*H*)-dione 4′-(*E*)-(*O*-methyloxime).
[e] If present, impurities moxidectin deoxydiene and 4′-methylthiomethoxymoxidectin may not be completely resolved by the method. These peaks are integrated together to determine conformance.

• TOTAL ORGANIC IMPURITIES

Analysis: Calculate the sum of all impurities found in the tests for *Organic Impurities: Early-Eluting Impurities* and *Organic Impurities: Late-Eluting Impurities* in the portion of Moxidectin taken.

Acceptance criteria: NMT 7.0%

SPECIFIC TESTS

• **WATER DETERMINATION ⟨921⟩,** *Method I*: NMT 1.3%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers, and store in a refrigerator.

Change to read:

• **LABELING:** Label it to indicate that it is for veterinary use only. ▲If it is intended for use in animals, it is so labeled.▲ (TBD) Label it to state the name(s) and amount(s) of any added substance(s).

• **USP REFERENCE STANDARDS ⟨11⟩**
USP Moxidectin RS
USP Moxidectin System Suitability Mixture RS