Moxidectin

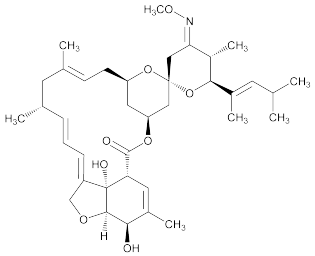
Type of Posting	Revision Bulletin
Posting Date	26–June–2018
Official Date	27–June–2018
Expert Committee	Chemical Medicines Monographs 3
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 3 Expert Committee has revised the Moxidectin monograph. The purpose of the revision is to revise the *Labeling* statement to allow flexibility for indications where products using the drug substance are intended for human use. Please note that the *Labeling* statement of the Revision Bulletin has been modified from the Notice of Intent to Revise posted on 27–Apr–2018.

The Moxidectin Revision Bulletin supersedes the currently official Moxidectin monograph.

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).

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:** ▲If it is intended for use in animals, it is so labeled.▲ (RB 27-Jun-2018) 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