CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210867Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: ***Approval***

NDA 210867
Review # 1

Drug Name/Dosage Form	Moxidectin Tablets*
Strength	2 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Medicines Development for Global Health
US agent, if applicable	Mary Shatzoff, MS, RAC

***** *No proprietary name approved at the time of this review*

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	October 13, 2017	All
Amendment (eCTD 005)	December 18, 2017	Drug Product
Amendment (eCTD 008)	January 22, 2018	Biopharmaceutics, Drug Product
Amendment (eCTD 010)	January 26, 2018	Drug Product, Process
Amendment (eCTD 011)	January 29, 2018	Drug Substance
Amendment (eCTD 012)	January 30, 2018	Process
Amendment (eCTD 013)	February 1, 2018	Labeling
Amendment (eCTD 015)	February 7, 2018	Process
Amendment (eCTD 018)	February 26, 2018	Drug Substance, Drug Product, Process, Biopharmaceutics
Amendment (eCTD 019)	March 6, 2018	Process
Amendment (eCTD 020)	March 13, 2018	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Katherine Windsor	Charles Jewell
Drug Product	Yong Wang	Balajee Shanmugam
Process	Ying Wang	Upinder Atwal
Microbiology*	Ying Wang	Upinder Atwal
Facilities	Ebern Dobbin	Derek Smith
Biopharmaceutics	Joan Zhao	Elsbeth Chikhale
Environmental Assessment**	Jim Laurenson	N/A
Regulatory Business Process Manager	Anh-Thy Lee	N/A
Application Technical Lead	Dorota Matecka	N/A

** The microbiology aspects of the drug product are assessed in the Process Chapter*

*** EA is covered in the Drug Product Chapter*

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Moxidectin	Adequate	March 9, 2018 (Panorama)	Review by Katherine Windsor

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	126876	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Adequate (*refer to DS and DP reviews*)		Jim Wild
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, moxidectin tablets. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on March 13, 2018. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality.

II. Summary of Quality Assessments

A. Product Overview

Moxidectin is a macrocyclic lactone of the milbemycin class derived from the actinomycete *Streptomyces cyanogriseus*. Moxidectin a broad-spectrum endectocide has been used commercially for veterinary use for over 25 years. However, it has not been approved for human use. This NDA provides for moxidectin tablets, 2 mg, which are indicated for the treatment of onchocerciasis due to (b) (4) *Onchocerca volvulus* in patients aged 12 years and older.

Proposed Indication(s) including Intended Patient Population	Treatment of onchocerciasis in patients 12 years old and older.
Duration of Treatment	A single dose of 8 mg (four 2 mg tablets) taken orally with or without food.
Maximum Daily Dose	8 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Moxidectin is a semisynthetic macrocyclic lactone of the milbemycin class. Moxidectin drug substance is described as white to pale yellow amorphous powder. Due to its low aqueous solubility, moxidectin drug substance (b) (4) The chemistry manufacturing and controls (CMC) information for moxidectin drug substance has been provided via a reference to DMF Type II (b) (4) DMF (b) (4) was reviewed in support of this NDA and was found to be acceptable (review dated March 9, 2018, in Panorama). The NDA includes comparative batch data for moxidectin drug substance manufactured by (b) (4) (the proposed commercial manufacturer) used to make drug product commercial batches and moxidectin drug

substance manufactured by (b) (4) . The data provided indicate comparability of the drug substance derived from the two sources; however, moxidectin produced by (b) (4) (the proposed commercial manufacturer) generally contains a lower level of impurities than the moxidectin used in (b) (4) Available stability data support a retest period of (b) (4) months for moxidectin drug substance stored at (b) (4).

The drug substance specification includes relevant quality attributes such as appearance, identity, assay, impurities, water content, residue on ignition (USP <281>), (b) (4) residual solvents and microbial limits. The DMF holder performed sufficient elemental impurities testing (USP <232>) to justify exclusion of routine testing. The routine testing (b) (4) Based on the overall information, the drug substance specification, as proposed in the NDA, was found acceptable by the Drug Substance Reviewer.

The proposed drug substance specification is based on the monograph for Moxidectin USP. Therefore, it will ensure that moxidectin released under this NDA will both meet the current USP standards and be adequate for human use. The USP monograph for moxidectin currently includes a statement “for veterinary use only”. (b) (4) The process of updating the moxidectin monograph is currently pending.

The drug product, moxidectin tablet, is an immediate release, uncoated, white to pale yellow, oval shaped tablet debossed with ‘AKKA’ on one side. Each tablet contains 2 mg of (b) (4) moxidectin and the following inactive ingredients: anhydrous lactose, sodium croscarmellose, microcrystalline cellulose, sodium lauryl sulfate, colloidal silicon dioxide, and magnesium stearate, all of which meet compendial standards.

The drug product specification includes tests and acceptance criteria for appearance, identity, (b) (4), uniformity of dosage units, assay, dissolution, disintegration time, degradation products, and microbial limits. During the review, several revisions to the proposed drug product specification were recommended by reviewers such as revision of the proposed acceptance criterion for dissolution (as discussed below), and acceptance criteria for impurities/degradation products (from NMT (b) (4) % to NMT (b) (4) % for individual specified degradation products, and from NMT (b) (4) % to NMT (b) (4) % for total degradation products). The proposed microbial control for the drug product was assessed by the Process Reviewer and found acceptable. The overall drug product specification, including the analytical procedures and validation data were found to be adequate. In addition, risk assessment regarding elemental impurities, as per USP <232>, was included in the NDA and found acceptable by the Drug Product Reviewer.

The commercial drug product packaging container closure system consists of a 120-cc white, high density polyethylene (HDPE) bottle with (b) (4) closure, induction seal liner, approximately 1.7 gram (b) (4) pharmaceutical coil (b) (4), and a 1 gram silica

gel (desiccant sachet). Each bottle contains 500 tablets. The proposed container closure system was found to be safe and suitable for the proposed commercial drug product.

Stability of the proposed drug product, moxidectin tablets, 2 mg, packaged in the proposed container closure system has been demonstrated through adequate 12-month long-term stability data (30°C/65% RH) and 6-month of data at 40°C/75% RH for three representative drug product batches. No significant changes in the assay values were observed, and only slight increase in impurities noted over the period of 12 months. In addition, (b) (4) Therefore, the proposed expiry dating of 12 months for the drug product, moxidectin tablets, 2 mg, packaged in HDPE bottles, and to be stored below 30°C (86°F), has been found acceptable. Additionally, the Applicant's claim of categorical exclusion from the Environmental Assessment per 21 CFR 25.31(b) has been found acceptable.

The manufacturing process for the drug product, moxidectin tablets, involves the followings steps: (b) (4)
The proposed drug product (moxidectin tablets) is considered a low-dose drug product as it contains only 2 mg of the drug substance per tablet. Therefore, the (b) (4) are important quality attributes to ensure safety and efficacy of the proposed drug product. During the NDA review, FDA recommended inclusion of additional in-process controls for future commercial drug product batches. Specifically, (b) (4)
by the Applicant, have been found acceptable. Overall information regarding the drug product manufacturing process provided in the original NDA submission and subsequent amendments has been found adequate by the Process Reviewer.

The biopharmaceutics review focused on the assessment of the proposed dissolution method and acceptance criteria, and need for bridging. Based on information provided, the proposed dissolution method was found acceptable. In addition, in vitro dissolution profiles provided for the drug product registration stability, clinical, and development batches were found comparable, although slower drug release was observed for the registration batches as compared with the clinical batch (used in the Phase I 1008 study). Based on the dissolution data from this clinical batch, the acceptance criterion of Q= (b) (4)% at 45 minutes was recommended by the FDA and accepted by the Applicant.

During the labeling review, a few revisions were recommended from the product quality perspective, such as listing the inactive ingredients in an alphabetical order in Section 11 and removing several unusual statements e.g., (b) (4)

(b) (4) in Section 16. The labels and package insert are currently under detailed review by the NDA review team.

The moxidectin drug substance manufacturer is (b) (4) and the drug product manufacturer is (b) (4). Several other facilities are listed in this NDA. (b) (4) is responsible for drug substance (b) (4) In addition, (b) (4) will perform the drug product dissolution and microbiological testing, respectively. Based on the review of the application and inspectional documents for all manufacturing sites listed in this NDA, it has been determined that there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. Therefore, the overall recommendation of "Approve" was entered into Panorama for this NDA by OPF on March 13, 2018.

C. Special Product Quality Labeling Recommendations (see labeling review)

D. Final Risk Assessment (see Attachment I)

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BIOPHARMACEUTICS

Product Background:
NDA: 210867 (505(b)(1))

Drug Product Name / Strength: Moxidectin Tablets, 2 mg

Route of Administration: Oral

Applicant Name: Medicines Development Limited

Review Summary:
The drug substance, moxidectin (a new molecular entity), is a macrocyclic lactone of the milbemycin class. This is the first application for use of Moxidectin in humans worldwide.

The drug substance, moxidectin, (b) (4) powder, has very low solubility in water and the solubility of moxidectin is not affected by pH. The proposed drug product is an immediate release uncoated tablet.

This review evaluates the proposed dissolution method, dissolution acceptance criterion, and the need for bridging.

Based on the provided dissolution data, the following dissolution method and revised acceptance criterion are acceptable and agreed upon:

Proposed Dissolution Method and Revised Acceptance Criterion	
Apparatus	USP II (Paddle)
Rotation Speed	65 RPM
Medium	0.074% Tween 20 in water
Volume	(b) (4) 500 mL
Acceptance Criterion	Q= (b) (4) % at 45 minutes

The drug product (batch 400070) used in Phase I study 1008 is the same as the proposed commercial formulation, presentation and drug product manufacturing site. The pharmacokinetic (PK) profiles of batch 400070 in Phase I 1008 study were compared to the PK profiles of the drug product used in the earlier clinical studies (Phase III Study and Phase I Study 1005). The OCP reviewer will evaluate the study results and thus no in vitro bridging is needed.

From the Biopharmaceutics perspective, NDA 210867 for Moxidectin Tablets, 2 mg is recommended for **APPROVAL**.

List of Submissions being reviewed:

Submission(s) Reviewed	**Document Date**
Original Submission	10/13/2017
Amendment (Stability data)	12/18/2017
IR Response	1/22/2018 and 2/26/2018

BCS Designation

The Applicant did not request an official BCS designation. The Applicant considers Moxidectin as a poorly soluble compound based on the Biopharmaceutical Classification System (BCS).

Drug Substance Solubility:

The Applicant states that the aqueous solubility of moxidectin is approximately 0.03 mg/L. The pH of a solution in 70% dioxane/water is 6.6. The solubility of moxidectin is not affected by pH since there are no functional groups on the molecule which are ionizable in the normal pH range of water Solubility of the drug substance is provided as shown below:

Table 1: Solubility of Moxidectin in Aqueous Solutions (mg/L)

Solubility in aqueous solutions (mg/L)	0.1 N HCl: 0.02 Acetate Buffer, pH 4.5: 0.04 Phosphate Buffer, pH 6.8: 0.02 Phosphate Buffer, pH 7.4: 0.03 Phosphate Buffer, pH 8.0: 0.03

Permeability:

The Applicant states that Moxidectin was shown to have high permeability using a rat perfusion model in isolated jejunum segments of anesthetized rats. However, no data is provided.

Drug Substance

Moxidectin is identified to have several polymorphic forms: (b) (4) [redacted]

Formulation:

The composition of the proposed commercial formulation, an immediate-release uncoated tablet is shown in Table 2, which is identical to the core tablet in the capsule (for blinding) used for clinical studies.

Table 2: Qualitative and Quantitative Composition of the Drug Product

Component	Quality Reference	Function	Quantity/Unit Dose (mg/tablet)
(b) (4) Moxidectin	USP	Active Ingredient	2.0
Microcrystalline Cellulose	NF	(b) (4)	
Anhydrous Lactose	NF		
Croscarmellose Sodium	NF		
Sodium Lauryl Sulfate	NF		
Colloidal Silicon Dioxide	NF		
Magnesium Stearate[a]	NF		
(b) (4)	NF		
Total Tablet Weight	--	--	**100.0**

[a] (b) (4)

USP: United States Pharmacopeia; NF: National Formulary; NA: Not Applicable

Dissolution Method and Acceptance Criteria

The original dissolution method (Method # 0093.00) was developed by (b) (4) as the dissolution medium. Based on the Type C CMC meeting held on February 14, 2017 [1], the Applicant optimized the dissolution method for improved discriminatory ability. The currently proposed dissolution testing parameters (Method # TP74879) are summarized below:

Proposed Dissolution method	
Apparatus	USP II (Paddle)
Rotation (rpm)	65
Medium	0.074% Tween 20 in (b) (4) water
Volume (mL)	500 mL

In the Pharmaceutical Development Report (Module 3.2.P.2.2.3), justification for the choice of dissolution apparatus, dissolution medium, and agitation speed are provided.

Dissolution Medium Volume

The Applicant selected a volume of 500 mL dissolution media, as it is a volume commonly used for immediate release tablets, especially for a drug product with a low drug load (2 mg in the 100 mg tablet) and results in increased peak height for quantitation purposes.

Dissolution Medium

Moxidectin is neutral across the physiologic pH range and possesses limited aqueous solubility in the absence of micellar solubilization. (b) (4) The Applicant evaluated a variety of surfactant systems and selected Tween 20 for further analysis, as shown in Table 3.

Table 3: Dissolution Media Evaluated During Development

Dissolution Media	Results
(b) (4)	
Tween 20 in water	Refer to Sections 1.4.2 and 1.4.3

[1] DARRTS: IND 126876 COR-MEET-03 (Meeting Minutes), final date 03/10/2017

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(b) (4)

[redacted]

Reviewer's Assessment of the dissolution method and method validation: Acceptable

The Applicant has adequately demonstrated the suitability of the dissolution method for batch release and stability testing. The dissolution method shows some potential ability to detect variation in the amount of Magnesium Stearate in the formulation. The proposed dissolution method's discriminating power with regards to other critical manufacturing variables was not demonstrated.

The proposed dissolution method (i.e. *US Apparatus II at 65 rpm using 500 mL 0.074% Tween 20 in water)* is found acceptable for the QC of the proposed drug product

Dissolution Acceptance Criterion:

The Applicant proposed a dissolution acceptance criterion of (b) (4) and provided the dissolution data from batch 400070 (Phase I clinical Study 1008), registration stability batches (400071, 400118 and 400119), and key development batches that have been stored for 5-11 months at various conditions as shown in Table 11 and 12. There is no dissolution data of Phase III batches (manufactured in October 2008 and September 2009) available using the proposed dissolution method (developed in 2017), as the Applicant claims that there were no supplies of the Phase III drug product remaining.

Table 6: Dissolution Results for Clinical and Process Development Batches of the proposed Drug Product (n=12)

(b) (4)

Table 7: Dissolution Results for Registration Stability Batches of Drug Product (n=12)

Packaged Batch/Use	Elapsed Time During Stability Storage/ Storage Condition	Time Point (minutes)	Range (n=12 vessels) (%)	Mean (%)	% RSD
400071/ Registration Stability	7.5 months/ 30°C, 65% RH	5	(b) (4)	42	14.4
		10		74	4.2
		15		80	1.8
		20		82	2.3
		30		84	3.3
		45		88	3.3
		60		90	3.5
400118/ Registration Stability	7.5 months/ 30°C, 65% RH	5		41	19.5
		10		68	6.7
		15		74	3.8
		20		77	2.5
		30		79	1.8
		45		82	1.8
		60		84	1.5
400119/ Registration Stability	7.5 months/ 30°C, 65% RH	5		39	17.1
		10		65	6.3
		15		73	5.5
		20		76	5.5
		30		78	4.4
		45		81	3.3
		60		84	3.1

RH: relative humidity; RSD: relative standard deviation

The Applicant note that for drug product batches 400070, PD17002, and PD17004, (b) (4) As the test method was implemented at the 6-month time point in the on-going registration stability program, the Applicant used dissolution results from the 6- and 9-month time points to establish the dissolution acceptance criterion.

Figure 7. Dissolution Profile for Registration Stability, Clinical and Process Development Batches of Moxidectin Tablets, 2 mg (n=12)

Reviewer's Assessment of the dissolution acceptance criterion:
Compared with the clinical batch 400070 (Appendix 4), slower drug release was observed for the registration batches (Appendix 5) using the proposed dissolution method. In the IR response dated January, 22, 2018, the Applicant stated that the observed slower drug release was due to the lower drug content in batch 400118 and 400119 (Appendix 1).

An acceptance criterion of Q (b) (4)% (Q) at 45 minutes was recommended in IRs dated January 12, 2018 and February 15, 2018 based on the dissolution data from the clinical batch 400070 (Phase I Study 1008) only. The revised acceptance criterion of Q= (b) (4)% (Q) at 45 minutes was agreed upon in the IR response dated February 26, 2018 (Appendix 2).

Bridging of Formulations:

(b) (4)

The oral solution formulation was compared with a 2 mg tablet formulation in a bioavailability study (Study 101). The 2 mg tablet formulation was then used for all subsequent clinical studies, including 4 additional Phase I studies, the Phase II and pivotal Phase III clinical study (Appendix 3). The drug product formulation for the Phase I study 1008 and planned commercial distribution are identical to that used in the Phase III study ONCBL60801 in 2007/2008, and all other clinical trials, except of the scale and manufacturing site (shown in Appendix 3). To support the equivalence for the *in vivo* performance of the drug product used in the Phase III study and drug product manufactured at the proposed commercial drug product site

using the commercial manufacturing process, the pharmacokinetic (PK) profiles of the proposed commercial drug product (batch 400070) in the Phase I study 1008 were compared to the PK profiles of the drug product used in the earlier clinical studies (Phase III Study and Phase I Study 1005). The OCP reviewer will evaluate the study results and no in vitro bridging is needed.

To maintain the blinding in the Phase II and Phase III clinical trials, over-encapsulation with opaque capsules was utilized to disguise both the treatment groups (moxidectin or ivermectin) to each subject. The formulation of the core moxidectin tablet, 2 mg used in the Phase III clinical study (ONCBL60801) is identical to the proposed commercial formulation. A comparison of the dissolution profile using the earlier dissolution method (i.e. 900 mL 0.4% SLS in water using USP 2 at 50 rpm) for the core tablets and over-encapsulated tablets was provided to demonstrate that the over-encapsulation does not impact the *in vitro* performance (Figure 8). The Applicant concluded that the over-encapsulation of the drug product does not appear to have a meaningful impact on the *in vitro* performance of the drug product. This is acceptable.

Figure 8. Mean Dissolution Results for Over-Encapsulated Tablets versus Core Tablets (b) (4)

R Regional Information

Comparability Protocols: None

Post-Approval Commitments: None

Lifecycle Management Considerations: None

List of Deficiencies: None

Recommendations:
From the Biopharmaceutics perspective, NDA 210867 for Moxidectin Tablets, 2 mg is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: *Zhuojun Joan Zhao 3/6/2018*

Secondary Reviewer Name and Date: *Elsbeth Chikhale, Ph.D. 3/9/2018*

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Elsbeth Chikhale

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LABELING

IQA Review Guide Reference

NDA 210867

I. Package Insert

1. *Highlights of Prescribing Information*

These highlights do not include all the information needed to use MOXIDECTIN safely and effectively. See full prescribing information for MOXIDECTIN.

MOXIDECTIN tablets, (b) (4) for oral use
Initial U.S. Approval: 2018

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	MOXIDECTIN
Dosage form, route of administration	MOXIDECTIN tablets, (b) (4) for oral use
Controlled drug substance symbol (if applicable)	Not Applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 2 mg

2. *Section 2 Dosage and Administration*

2.1 Recommended Dosage in Patients 12 Years of Age and Older
The recommended dose of MOXIDECTIN (b) (4) is a single dose of 8 mg (four 2 mg tablets) taken orally with or without food [see Clinical Pharmacology (12.3)].

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Not Applicable

3. *Section 3 Dosage Forms and Strengths*

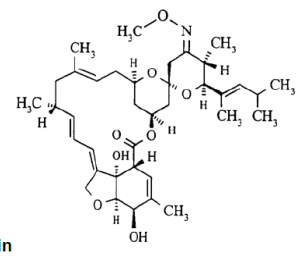
Moxidectin tablets are available as white to pale yellow uncoated oval-shaped tablets, debossed on one side with "AKKA". Each tablet contains 2 mg moxidectin.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablets
Strengths: in metric system	2 mg
Active moiety expression of strength with equivalence statement (if applicable)	Not Applicable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	white to pale yellow uncoated oval-shaped tablets, debossed on one side with "AKKA"

4. *Section 11 Description*

MOXIDECTIN tablets contain moxidectin, a macrocyclic lactone of the milbemycin class derived from the actinomycete Streptomyces cyanogriseus.

The chemical name of moxidectin is (2aE,4E,5'R,6R,6'S,8E,11R,13S,15S,17aR,20R,20aR,20bS)-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-2H,13H,17H-furo[4,3,2-pq][2,6]benzodioxacyclooctadecin-13,2'-[2H]pyran]-4',17(3'H)-dione 4'-(E)-(O-methyloxime).

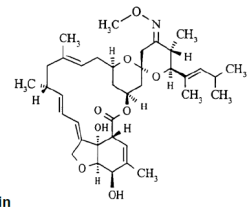


Moxidectin

Moxidectin is a white or pale-yellow, amorphous powder, formula $C_{37}H_{53}NO_8$ and molecular weight 639.82 Dalton. Moxidectin is readily soluble in organic solvents such as methylene chloride, diethyl ether, ethanol, acetonitrile, and ethyl acetate. It is only slightly soluble in water (0.51 mg/L) and the melting point range for moxidectin powder is 145°C to 154°C.

MOXIDECTIN tablets are for oral administration. Each tablet contains 2 mg of moxidectin. The tablets are uncoated and include the following inactive ingredients: microcrystalline cellulose, lactose anhydrous, sodium lauryl sulfate, colloidal silicon dioxide, croscarmellose sodium and magnesium stearate.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	MOXIDECTIN
Dosage form and route of administration	MOXIDECTIN tablets are for oral administration.
Active moiety expression of strength with equivalence statement (if applicable)	Not Applicable
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	The tablets are uncoated and include the following inactive ingredients: microcrystalline cellulose, lactose anhydrous, sodium lauryl sulfate, colloidal silicon dioxide, croscarmellose sodium and magnesium stearate. To list the inactive ingredients in alphabetical order, the following should be recommended to the applicant: *The tablets are uncoated and include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose anhydrous, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.*
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	a macrocyclic lactone of the milbemycin class derived from the actinomycete *Streptomyces cyanogriseus*.

Chemical name, structural formula, molecular weight	(2aE,4E,5'R,6R,6'S,8E,11R,13S,15S,17aR,20R,20aR,20bS)-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-2H,13H,17H-furo[4,3,2-pq][2,6]benzodioxacyclooctadecin-13,2'-[2H]pyran]-4',17(3'H)-dione 4'-(E)-(O-methyloxime) Formula: $C_{37}H_{53}NO_8$ Molecular weight: 639.82 Dalton  Moxidectin
If radioactive, statement of important nuclear characteristics.	Not Applicable
Other important chemical or physical properties (such as pKa or pH)	Moxidectin is readily soluble in organic solvents such as methylene chloride, diethyl ether, ethanol, acetonitrile, and ethyl acetate. It is only slightly soluble in water (0.51 mg/L) and the melting point range for moxidectin powder is 145°C to 154°C.

5. ***Section 16 How Supplied/Storage and Handling***

MOXIDECTIN tablets containing 2 mg moxidectin are white to pale yellow uncoated oval-shaped tablets, debossed on one side with "AKKA". Each high-density polyethylene bottle contains 500 tablets (NDC 71705-050-01), a silica gel desiccant and polyester coil.

Store below 30 °C (86 °F).

- Protect from light.
- (b) (4)
- Once open, the full contents of the container should be used within 24 hours with any unused content discarded.

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	MOXIDECTIN tablets containing 2 mg moxidectin
Available units (e.g., bottles of 100 tablets)	Each high-density polyethylene bottle contains 500 tablets (NDC 71705-050-01), a silica gel desiccant and polyester coil.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to pale yellow uncoated oval-shaped tablets, debossed on one side with "AKKA" NDC 71705-050-01
Special handling (e.g., protect from light)	Protect from light. (b) (4) Once open, the full contents of the container should be used within 24 hours with any unused content discarded. (b) (4)
Storage conditions	Store below 30 °C (86 °F)
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: Medicines Development for Global Health, Melbourne, Victoria, Australia

Reviewer's Assessment of Package Insert: *{Adequate/Inadequate}*

All CMC related deficiencies listed in the package insert for sections of Highlights of Prescribing Information, Dosage and Administration, Dosage of Forms and Strengths, and Description have been discussed in a labeling meeting dated 2/27/2018 and communicated to the applicant. Since moxidectin droes not belong to any class as described in the Labeling Review Tool but a semisythetic fermentation derived molecule and therefore it should be labeled and handled with the same precautions applied for other approved anti-infective drugs.

In the last of paragraph of Section 16 How Supplied/Storage and Handling, the following should be deleted:

(b) (4)

- ***Any deficiencies should be listed at the end in the "List of Deficiencies"***

II. Labels:

1. ***Container and Carton Labels***

(b) (4)

{Copy/paste or refer to a representative example of a proposed container}

2. ***Carton Label***

N/A

{Copy/paste or refer to a representative example of a proposed carton labels}

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4) (moxidectin) tablets	Not applicable
Dosage strength	2 mg	Not applicable
Net contents	500 tablets	Not applicable
"Rx only" displayed prominently on the main panel	"Rx only"	Not applicable
NDC number (21 CFR 207.35(b)(3)(i))	The space for NDC number is available.	Not applicable
Lot number and expiration date (21 CFR 201.17)	The space for lot number and expiration is available	Not applicable
Storage conditions	Store below 30 °C (86 °F) Protect from light	Not applicable
Bar code (21CFR 201.25)	Bar code is available.	Not applicable
Name of manufacturer/distributor	Manufactured for: Medicines Development for Global Health, Melbourne, Australia	Not applicable
And others, if space is available	This is a bulk package not intended for household use	

Reviewer's Assessment of Labels: ***{Adequate/Inadequate}***

As suggested by Dr. Deborah Myers from DMEPA, include the following statement in the container label.

(b) (4)

- ***Any deficiencies should be listed at the end in the "List of Deficiencies"***

List of Deficiencies:

In the last of paragraph of Section 16 How Supplied/Storage and Handling, the following should be deleted:

(b) (4)

In your container label, include the following statement:

(b) (4)

Overall Assessment and Recommendation:

The proposed PI and container label are acceptable from a CMC perspective upon resolving the above package insert and container deficiencies.

Primary Labeling Reviewer Name and Date:

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Yong Wang

Digitally signed by Yong Wang
Date: 3/16/2018 11:14:17AM
GUID: 508da7210002a01861739fd87b35adb9

Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 3/16/2018 05:05:18PM
GUID: 50758d5000003c1b1962e036ea11002c

ATTACHMENT I: Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability of moxidectin	Formulation Raw materials Process parameters Scale/equipment Site	L	Adequate specification for the drug substance and drug product	Acceptable	
Content uniformity	Formulation Raw materials Process parameters Scale/equipment Site	M	(b) (4)	Acceptable	
Physical stability	Formulation Raw materials Process parameters Scale/equipment Site	L	Additional information requested and sufficient XRPD data provided during the NDA review	Acceptable	
Microbial limits	Formulation Raw materials Process parameters Scale/equipment Site	L	Microbial limits testing conducted at release and end of shelf life	Acceptable	
Dissolution	Formulation Raw materials Process parameters Scale/equipment Site	L	The dissolution method was found adequate; the acceptance criterion for drug product release and stability test was revised and found adequate	Acceptable	

NDA OVERALL RECOMMENDATION:
This NDA is recommended for Approval from the Product Quality perspective.
On behalf of OPQ Team
Dorota Matecka, ATL for NDA 210867

Dorota M. Matecka -S