

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210867Orig1s000

LABELING

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, for oral use

Initial U.S. Approval: 2018

-----INDICATIONS AND USAGE-----

Moxidectin is an anthelmintic indicated for the treatment of onchocerciasis due to *Onchocerca volvulus* in patients aged 12 years and older. (1)

Limitations of Use:

- Moxidectin Tablets do not kill adult *O. volvulus* parasites. Follow-up is advised.
- The safety and efficacy of repeat administration of Moxidectin Tablets in patients with *O. volvulus* has not been studied.

-----DOSAGE AND ADMINISTRATION-----

Patients aged 12 years and older: Take 8 mg (four 2 mg tablets) as a single oral dose, with or without food. (2.1)

-----DOSAGE FORMS AND STRENGTHS-----

Tablets: 2 mg. (3)

-----CONTRAINDICATIONS-----

None. (4)

-----WARNINGS AND PRECAUTIONS-----

- Cutaneous, Ophthalmological and/or Systemic Adverse Reactions of Varying Severity (Mazzotti Reaction): This may occur in patients with onchocerciasis following treatment with

Moxidectin Tablets. Monitor patients for symptoms, including symptomatic orthostatic hypotension. (5.1)

- Symptomatic Orthostatic Hypotension: Episodes of symptomatic orthostatic hypotension including inability to stand without support may occur in patients following treatment with Moxidectin Tablets. (5.2)
- Encephalopathy in *Loa loa* co-infected patients: Serious or even fatal encephalopathy following treatment with Moxidectin Tablets may occur in patients co-infected with *Loa loa*. Assess patients for loiasis in *Loa loa* endemic areas prior to treatment. (5.3)
- Edema and Worsening of Onchodermatitis: Patients with hyper-reactive onchodermatitis (sowda) may be more likely than others to experience severe edema and aggravation of onchodermatitis. (5.4)

-----ADVERSE REACTIONS-----

The most common adverse reactions (incidence > 10%) were: eosinophilia, pruritus, musculoskeletal pain, headache, lymphopenia, tachycardia, rash, abdominal pain, hypotension, pyrexia, leukocytosis, influenza-like illness, neutropenia, cough, lymph node pain, dizziness, diarrhea, hyponatremia and peripheral swelling. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Medicines Development for Global Health at 1-800-MDGH-456 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing in Patients Aged 12 Years and Older

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Cutaneous, Ophthalmological and/or Systemic Adverse Reactions

5.2 Symptomatic Orthostatic Hypotension

5.3 Encephalopathy in *Loa loa* Co-infected Patients

5.4 Edema and Worsening of Onchodermatitis

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Moxidectin Tablets are indicated for the treatment of onchocerciasis due to *Onchocerca volvulus* in patients aged 12 years and older [see *Clinical Studies* (14)].

Limitations of Use:

Moxidectin Tablets do not kill adult *O. volvulus*. Follow-up evaluation is advised.

The safety and efficacy of repeat administration of Moxidectin Tablets in patients with *O. volvulus* has not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Patients Aged 12 Years and Older

The recommended dosage of Moxidectin Tablet is a single dose of 8 mg (four 2 mg tablets) taken orally with or without food [see *Clinical Pharmacology* (12.3)].

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 of moxidectin.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cutaneous, Ophthalmological and/or Systemic Adverse Reactions

Treatment with Moxidectin Tablets may cause cutaneous, ophthalmological and/or systemic reactions of varying severity (Mazzotti reaction). These adverse reactions are due to allergic and inflammatory host responses to the death of microfilariae [see *Adverse Reactions* (6.1)]. There is a trend toward an increased incidence of these adverse reactions in patients with higher microfilarial burden.

The clinical manifestations of Mazzotti reaction includes pruritus, headache, pyrexia, rash, urticaria, hypotension (including symptomatic orthostatic hypotension and dizziness) [see *Warnings and Precautions* (5.2)], tachycardia, edema, lymphadenopathy, arthralgia, myalgia, chills, paresthesia and asthenia. Ophthalmological manifestations include conjunctivitis, eye pain, eye pruritus, eyelid swelling, blurred vision, photophobia, changes in visual acuity, hyperemia, ocular discomfort and watery eyes. These adverse reactions generally occur and resolve in the first week post-treatment. Laboratory changes include eosinophilia, eosinopenia, lymphocytopenia, neutropenia, and increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT) and lactate dehydrogenase (LDH). Proteinuria has also been reported.

Treatment of severe Mazzotti reactions has not been evaluated in controlled clinical trials. Symptomatic treatments such as oral hydration, recumbency, intravenous normal saline, and/or parenteral corticosteroids have been used to treat orthostatic hypotension. Antihistamines and/or analgesics have been used for most mild to moderate cases.

5.2 Symptomatic Orthostatic Hypotension

An increased number of patients who received Moxidectin Tablets developed symptomatic orthostatic hypotension with inability to stand without support after lying down for 5 minutes (in an orthostatic hypotension provocation test); 47/978 (5%) compared with 8/494 (2%) who received ivermectin. The decreases in blood pressure were transient, managed by resumption of recumbency and most commonly occurred on Days 1 and 2 post-treatment. Advise patients that if they feel dizzy or light-headed after taking Moxidectin Tablets, they should lie down until the symptoms resolve.

5.3 Encephalopathy in *Loa loa* Co-infected Patients

Patients with onchocerciasis who are also infected with *Loa loa* may develop a serious or even fatal encephalopathy following treatment with Moxidectin Tablets.

Moxidectin Tablets have not been studied in patients co-infected with *Loa loa*. Therefore, it is recommended that individuals who warrant treatment with Moxidectin Tablets and have had exposure to *Loa loa*-endemic areas undergo diagnostic screening for loiasis prior to treatment.

5.4 Edema and Worsening of Onchodermatitis

Patients with hyper-reactive onchodermatitis (sowda) may be more likely than others to experience severe edema and worsening of onchodermatitis following the use of Moxidectin Tablets. Symptomatic treatment has been used to manage patients who have experienced edema and worsening of onchodermatitis.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described in greater detail in other labeling sections:

- Cutaneous, Ophthalmological and/or Systemic Adverse Reactions [see *Warnings and Precautions* (5.1)]
- Symptomatic Orthostatic Hypotension [see *Warnings and Precautions* (5.2)]
- Encephalopathy in *Loa loa* Co-infection [see *Warnings and Precautions* (5.3)]
- Edema and Worsening of Onchodermatitis [see *Warnings and Precautions* (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under varying controlled conditions, adverse reaction rates observed in one clinical trial cannot be directly compared to rates observed in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of Moxidectin Tablets was evaluated in two randomized, double-blind, active-controlled studies (Trial 1 and Trial 2) [see *Clinical Studies* (14)]. In Trial 1, 978 patients received Moxidectin Tablets as a single oral dose of 8 mg and 494 patients received ivermectin as a single oral dose of approximately 150 mcg/kg. In Trial 2, 127 patients received Moxidectin Tablets as a single oral dose ranging from 2 mg (this is not an approved dose) to 8 mg (38 received the recommended 8 mg dose) and 45 patients received ivermectin as a single oral dose of approximately 150 mcg/kg.

Most Common Adverse Reactions

No patients withdrew from either trial due to adverse reactions. Adverse Reactions reported in Trial 1 in > 10% of patients are summarized in Table 1. Most were related to physical, vital signs and laboratory changes associated with Mazzotti reaction [see *Warnings and Precautions* (5.1)].

Table 1: Adverse Reactions Occurring in > 10% of Moxidectin-treated Patients with Onchocerciasis in Trial 1

Adverse Reaction	Moxidectin N = 978 n (%)	Ivermectin N = 494 n (%)
Eosinophilia	721 (74)	390 (79)
Pruritus	640 (65)	268 (54)
Musculoskeletal pain ^a	623 (64)	257 (52)
Headache	566 (58)	267 (54)
Lymphocytopenia*	470 (48)	215 (44)
Tachycardia ^b	382 (39)	148(30)
Orthostatic tachycardia ^c	333 (34)	130 (26)
Non-orthostatic tachycardia ^d	179 (18)	57 (12)
Rash ^e	358 (37)	103 (21)
Abdominal pain ^f	305 (31)	173 (35)

Adverse Reaction	Moxidectin N = 978 n (%)	Ivermectin N = 494 n (%)
Hypotension ^g	289 (30)	125 (25)
Orthostatic hypotension ^h	212 (22)	81 (16)
Pyrexia/Chills	268 (27)	88 (18)
Leukocytosis	240 (25)	125 (25)
Influenza like illness	226 (23)	102 (21)
Neutropenia**	197 (20)	112 (23)
Cough	168 (17)	88 (18)
Lymph node pain	129 (13)	28 (6)
Dizziness	121 (12)	44 (9)
Diarrhea/Gastroenteritis/Enteritis	144 (15)	84 (17)
Hyponatremia	112 (12)	65 (13)
Peripheral swelling	107 (11)	30 (6)

^a Includes "myalgia", "arthralgia", "musculoskeletal pain", "pain" and "back pain"

^b Includes "orthostatic heart rate increased", "postural orthostatic tachycardia syndrome", "heart rate increased" and "sinus tachycardia"

^c Includes "orthostatic heart rate increased" and "postural orthostatic tachycardia syndrome"

^d Includes "heart rate increased", "tachycardia", and "sinus tachycardia"

^e Includes "rash", "papular rash" and "urticaria"

^f Includes "abdominal pain", "abdominal pain upper" and "abdominal pain lower"

^g Includes "orthostatic hypotension", "blood pressure orthostatic decreased", "blood pressure decreased", "mean arterial pressure decreased", "hypotension"

^h Includes "orthostatic hypotension", and "blood pressure orthostatic decreased"

*Lymphocytopenia is defined as absolute lymphocyte count less than $1 \times 10^9/L$

**Neutropenia is defined as absolute neutrophil count less than $1 \times 10^9/L$

The most common adverse reactions in patients (n = 38) treated with 8 mg moxidectin in Trial 2 were similar to the adverse reactions noted in Trial 1 described in Table 1 above.

Other Adverse Reactions Reported in Clinical Trials

The following adverse reactions occurred in less than 10% of subjects receiving Moxidectin Tablets in Trial 1:

Ocular Adverse Reactions: In Trial 1, the most common ocular adverse reactions (occurring in $\geq 0.5\%$ of patients) is shown in Table 2.

Table 2: Ocular Adverse Reactions Occurring in $\geq 0.5\%$ Moxidectin-treated Patients

Adverse Reaction	Moxidectin N = 978 n (%)	Ivermectin N = 494 n (%)
Eye pain	78 (8)	28 (6)
Eye pruritus	64 (7)	26 (5)
Visual impairment*	25 (3)	9 (2)
Eyelid edema	21 (2)	5 (1)
Conjunctivitis allergic	19 (2)	11 (2)
Ocular discomfort**	18 (2)	11 (2)
Ocular and conjunctival hyperemia	17 (2)	3 (1)
Lacrimation increased	13 (1)	10 (2)

*Includes "visual impairment", "blurred vision" and "low vision acuity"

**Includes "foreign body sensation", "ocular discomfort" and "abnormal sensation in the eye"

Hepatobiliary Adverse Reactions

More patients in the moxidectin arm experienced elevation in bilirubin above the upper limit of normal and elevation in transaminases > 5x upper limit of normal. Twenty-seven (2.8%) patients in the moxidectin arm and 3 (0.6%) patients in the ivermectin arm had hyperbilirubinemia. Most of the patients had single measurements of hyperbilirubinemia without concurrent elevation in transaminases.

Nine (1%) patients in the moxidectin arm and 2 (0.4%) patients in the ivermectin arm had elevation in ALT of more than 5x upper limit of normal; ten (1%) patients in the moxidectin arm and 3 (0.6%) patients in the ivermectin arm had elevation in AST to more than 5x upper limit of normal.

Laboratory Abnormalities

Laboratory abnormalities occurring in at least 1% of patients in the Trial 1 are described in Table 3.

Table 3: Laboratory Abnormalities in at least 1% of Moxidectin-treated Patients

Parameter	MOXIDECTIN (N = 978) n (%)	Ivermectin (N = 494) n (%)
Hematology		
Severe eosinophilia (> 5 x10 ⁹ /L)	173 (18)	111 (23)
Grade 3 lymphocytopenia (< 0.5 x10 ⁹ /L)	220 (23)	98 (20)
Grade 4 Neutrophils (< 0.5 x10 ⁹ /L)	65 (7)	46 (9)
Eosinopenia (<0.045 x10 ⁹ /L)	51 (5)	21 (4)
Hepatobiliary		
GGT (> 5x upper limit of normal)	26 (3)	16 (3)
Bilirubin (> 2x upper limit of normal)	14 (1.4)	2 (0.4)
AST (> 5x upper limit of normal)	10 (1)	3 (0.6)
ALT (> 5x upper limit of normal)	9 (1)	2 (0.4)

7 DRUG INTERACTIONS

Midazolam (CYP3A4 substrate)

In healthy subjects, concomitant administration of a single 8 mg oral dose of Moxidectin Tablets did not have an effect on the pharmacokinetics of midazolam [see *Clinical Pharmacology* (12.3)]. Moxidectin can be co-administered with CYP3A4 substrates.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data on the use of Moxidectin Tablets in pregnant women are insufficient to establish whether there is a moxidectin-associated risk for major birth defects and miscarriage. Moxidectin administered orally to pregnant rats during the period of organogenesis (Gestation Days (GD) 6 to 15), was not associated with significant embryo-fetal developmental effects at doses of approximately 15 times the recommended human dose based on body surface area. When moxidectin was dosed orally to pregnant rabbits during the period of organogenesis (GD 7 - 19), no embryo-fetal developmental effects were observed at oral doses of moxidectin up to 24 times the recommended human dose based on body surface area [see *Data*].

Daily parental oral administration of dietary moxidectin to rats prior to mating, and through mating, gestation, and lactation was associated with decreased survival and body weights for first-generation offspring without maternal toxicity at moxidectin doses less than 2-times the recommended human dose based on body surface area comparison. Daily dietary moxidectin did not produce maternal toxicity or adverse effects for first- and second-generation offspring at doses approximately equivalent to the recommended human dose based on

body surface area comparison. Offspring were assessed for survival, body weights, and fertility. Developmental milestones were not assessed in this study.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a rat embryo-fetal development study, daily oral administration of moxidectin at 12 mg/kg/day (approximately 15 times the recommended human dose of 8 mg based on body surface area comparison) during Gestation Days (GDs) 6 to 15 significantly increased the fetal incidence, but not the litter incidence of cleft palate and the fetal and litter incidence of a skeletal variation, wavy ribs, at a maternally toxic dose. Mean maternal food consumption, body weights, and body weight gain were significantly decreased at moxidectin doses of 10 and 12 mg/kg/day compared to control values. The no observed adverse effect level (NOAEL) value for maternal and fetal toxicity was considered to be 5 and 10 mg/kg/day respectively (approximately 6 and 12 times, respectively, the recommended human dose based on body surface area comparison). In the rabbit, daily oral administration of moxidectin at ≥ 5 mg/kg/day from GD7 to GD19 was not associated with fetal weight loss or malformations but resulted in significantly decreased maternal food consumption and body weight gains. The NOAEL value for maternal and fetal toxicity in the rabbit was 1 mg/kg/day and 10 mg/kg/day respectively (approximately 2 times and 24 times, respectively, the recommended human dose based on body surface area comparison). In a pre-postnatal study in rats, parental oral administration of dietary moxidectin prior to mating, through mating, gestation, and lactation did not produce adverse effects in first-generation or second-generation offspring at a maternal NOAEL dose of 0.824 mg/kg/day (approximately equivalent to the recommended human dose based on body surface area comparison). However, at moxidectin doses ≥ 1.1 mg/kg/day (approximately equivalent to 1.3 times the recommended human dose based on body surface area comparison), the survival and body weights of first-generation offspring were significantly decreased during the lactation period, and the number of live fetuses at birth was significantly decreased with a maternal moxidectin dose of 11 mg/kg/day (approximately equivalent to 13 times the recommended human dose based on body surface area comparison). In this study, offspring were assessed for survival, body weights, and fertility, and developmental milestones were not assessed.

8.2 Lactation

Risk Summary

Moxidectin was detected in the milk of lactating women following a single 8 mg dose of Moxidectin Tablets [see Data]. There are no data on the effects of Moxidectin Tablets on the breast-fed infant or milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Moxidectin Tablets and any potential adverse effects on the breastfed child from Moxidectin Tablets or from the underlying maternal condition.

Data

A pharmacokinetic study in twelve healthy adult lactating women who were 21 to 100 weeks post partum evaluated the concentrations of moxidectin in plasma and breast milk collected over a period of 28 days following a single 8 mg dose of Moxidectin Tablets. The mean ($\pm$ SD) exposure ratio of moxidectin present in human breast milk to that of human plasma was approximately 1.77 ($\pm$ 0.66) over a collection period of 28 days. The estimated mean ($\pm$ SD) total infant dose, assuming the infants would consume all the breast milk collected during the study, was 0.056 mg ($\pm$ 0.024 mg), which would be approximately 0.70% ($\pm$ 0.30%) of the maternal dose. The effects of moxidectin or its metabolites on the breast-fed child or milk production were not evaluated.

8.4 Pediatric Use

The safety and effectiveness of Moxidectin Tablets have been established in pediatric patients 12 years of age and older. In Trial 1, (n = 53 patients aged 12 to 17 years), the safety and effectiveness was similar to that observed in adults [see *Adverse Reactions (6.1)*, and *Clinical Studies (14)*]. The safety and effectiveness of Moxidectin Tablets in pediatric patients under 12 years of age has not been established.

8.5 Geriatric Use

Of the total number of patients included in Trial 1 that were treated with Moxidectin Tablets, 83 were aged 65 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out [see *Clinical Studies (14)* and *Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

No dose adjustment of Moxidectin Tablets is necessary for patients with mild (creatinine clearance (CrCL) 60 to 89 mL/min) to moderate (CrCL 30 to 59 mL/min) renal impairment. The safety of Moxidectin Tablets in patients with severe renal impairment (CrCL 15 to 29 mL/min) or end stage renal disease, is unknown [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

No specific antidote is available for overdose with Moxidectin Tablets. If overdose occurs, the patient should be monitored for evidence of toxicity. Treatment of overdose with Moxidectin Tablets consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Supportive therapy, if indicated, should include parenteral fluids and electrolytes, respiratory support (oxygen and mechanical ventilation if necessary) and pressor agents if clinically significant hypotension is present.

11 DESCRIPTION

Moxidectin Tablets contain moxidectin, an anthelmintic drug and 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). The structural formula is:

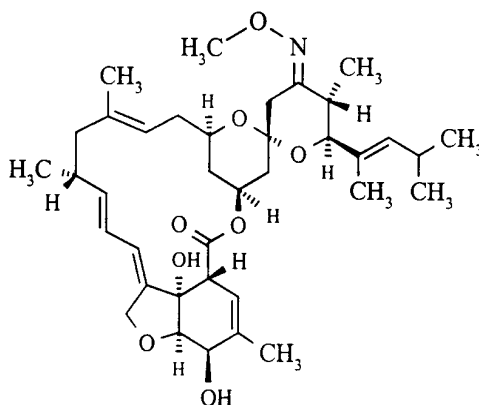


Figure 1: Moxidectin Structure

Moxidectin is a white or pale-yellow, amorphous powder. The empirical formula is $C_{37}H_{53}NO_8$ and the molecular weight is 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: colloidal silicon dioxide, croscarmellose sodium, lactose anhydrous, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Moxidectin, a macrocyclic lactone, is an anthelmintic drug [see *Microbiology (12.4)*].

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose 4.5 times the approved recommended dose, moxidectin does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetic parameters of moxidectin following a single 8 mg oral dose of Moxidectin Tablets to healthy subjects and patients with onchocerciasis under fasted conditions are shown in Table 4. Mean moxidectin C_{max} and AUC increased approximately proportionally to dose over a dose range of 2 to 36 mg (0.25 to 4.5 times the approved recommended dose) in healthy subjects under fasted conditions.

Table 4: Mean ($\pm$ SD) Pharmacokinetic Parameters of Moxidectin Following a Single 8 mg Oral Dose of Moxidectin Tablets to Healthy Subjects and Patients with Onchocerciasis Under Fasted Conditions

PK Parameter	Healthy Subjects (N = 27)	Patients with Onchocerciasis (N = 31)
C_{max} (ng/mL)	58.9 $\pm$ 12.5	63.1 $\pm$ 20.0
T_{max}^* (hours)	4 (2, 8)	4 (1, 4)
AUC _{inf} (ng•h/mL)	3387 $\pm$ 1328	2738 $\pm$ 1606
Half-life (hours)	784 $\pm$ 347	559 $\pm$ 525

C_{max} = maximum plasma concentration; T_{max} = time to reach C_{max} ; AUC_{inf} = area under the plasma concentration-time curve from time 0 to infinity;

* Median (range)

Absorption

Effect of Food

Moxidectin mean C_{max} and AUC increased on average by 34% and 39%, respectively, when administered with a standard high fat meal (900 calories, with a nutritional distribution of approximately 55% fat, 31% carbohydrates and 14% protein), compared to fasted conditions [see *Dosage and Administration (2.1)*].

Distribution

The apparent mean $\pm$ SD volume of distribution of moxidectin is 2421 $\pm$ 1658 L in patients with onchocerciasis. The plasma protein binding in humans is unknown.

Elimination

The mean terminal half-life of moxidectin in patients with onchocerciasis is 23.3 days (559 hours) following a single 8 mg dose of Moxidectin Tablets.

The apparent mean $\pm$ SD total clearance of moxidectin is approximately 3.50 $\pm$ 1.23 L/hour in patients with onchocerciasis.

Metabolism

The hepatic metabolism of moxidectin is minimal.

Excretion

Following administration of a single 8 mg oral dose of Moxidectin Tablets to healthy subjects, 2% of the dose is eliminated unchanged in the feces within the first 72 hours. Renal elimination of intact drug is negligible.

Specific Populations

In clinical studies, no clinically significant differences in the pharmacokinetics of moxidectin were observed based on age (18 to 60 years), sex, weight (42.7 to 107.2 kg), or renal impairment (creatinine clearance (CrCL) 47 to 89 mL/min, estimated by Cockcroft-Gault). The pharmacokinetics of moxidectin in patients with CrCL less than 47 mL/min is unknown. The pharmacokinetics of moxidectin in patients with hepatic impairment is unknown.

Patients with Renal Impairment

Based on a population pharmacokinetic analysis and the fact that renal elimination of intact drug is negligible, mild (creatinine clearance (CrCL), estimated by Cockcroft-Gault of 60 to 89 mL/min) and moderate (CrCL 30 to 59 mL/min) renal impairment is not likely to have an impact on the exposure of moxidectin. The effect of severe renal impairment (CrCL 15 to 29 mL/min) or of end-stage renal disease on the pharmacokinetics of moxidectin is unknown.

Drug Interaction Studies

Clinical Study with Midazolam (CYP3A4 substrate)

Co-administration of a single 8 mg dose of Moxidectin Tablets with a single oral 7.5 mg dose of midazolam (a sensitive CYP3A substrate) to healthy subjects (n = 37) did not affect the pharmacokinetics of midazolam or its major metabolite, 1-hydroxy midazolam.

In Vitro Studies

CYP Enzymes: Moxidectin is not a substrate or inhibitor of CYP enzymes.

Uridine 5'-diphospho-glucuronosyltransferases (UGTs): Moxidectin is not a UGT substrate.

Transporter Systems: Moxidectin is not a substrate of P-glycoprotein (P-gp) nor breast cancer resistance protein 1 (BCRP1).

12.4 Microbiology

Mechanism of Action

The mechanism by which moxidectin exhibits its effect against *O. volvulus* is not known. Studies with other nematodes suggest that moxidectin binds to glutamate-gated chloride channels (GluCl), gamma-aminobutyric acid (GABA) receptors and/or ATP-binding cassette (ABC) transporters. This leads to increased permeability, influx of chloride ions, hyperpolarization and muscle paralysis. Additionally, there is a reduction in motility of all stages of the parasite, excretion of immunomodulatory proteins, and the fertility of both male and female adult worms.

Antimicrobial activity

Moxidectin is active against the microfilariae of *O. volvulus* [see *Clinical Studies* (14)].

Studies suggest that moxidectin is not effective in killing the adult worms, however, it inhibits intra-uterine embryogenesis and release of microfilariae from the adult worms.

Resistance

Studies *in vitro* and infected animals suggest a potential for development of resistance to moxidectin and cross-resistance with other macrocyclic lactones, such as ivermectin. However, the clinical relevance of these findings is not known.

The mechanism of resistance may be multifactorial that include alteration in the target GluCl, GABA receptors and/or ABC transporters.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity effects for moxidectin have not been established.

Moxidectin was shown to be negative for genotoxicity in a battery of *in vitro* assays including a bacterial mutagenicity assay, mouse lymphoma cell mutagenicity assay, unscheduled DNA synthesis assay, and a chromosome aberration assay, as well as *in vivo* in a micronucleus assay in mice and a chromosome aberration assay in rats.

In fertility evaluations, male and female mating and fertility indices were not inhibited by oral-dietary moxidectin doses of approximately 0.86 mg/kg/day which is approximately equivalent to the recommended human dose based on body surface area comparison.

13.2 Animal Toxicology and/or Pharmacology

Moxidectin was associated with transient CNS-related clinical signs. In rats, a single dose of 20 mg/kg (equivalent to approximately 24 times the recommended human dose based on body surface area comparison) moxidectin was associated with piloerection, reduced arousal and body tone, abnormal gait, slowed breathing, and impaired righting reflex. In dogs, repeated doses of 1.6 mg/kg/day moxidectin (equivalent to approximately 7 times the recommended human dose based on body surface area comparison) was associated with lacrimation, languid appearance, tremors, slight salivation, and slight ataxia.

14 CLINICAL STUDIES

The assessment of the safety and efficacy of Moxidectin Tablets 8 mg in the treatment of onchocerciasis is based on data from two randomized, double-blind, active-controlled trials in patients with *O. volvulus* infection, Trial 1 in 1472 patients (NCT 00790998), and Trial 2, a dose-ranging trial (NCT 00300768). Patients in the trials received a single oral dose of moxidectin or ivermectin, the active control medication.

Efficacy was assessed by skin microfilarial density (microfilariae/mg skin) from the mean of 4 skin snips per person per time point up to 18 months post-treatment.

Trial 1 recruited adult and adolescent patients ≥ 12 years with a body weight ≥ 30 kg and ≥ 10 microfilariae/mg skin. Mean ($\pm$ SD) age was 42.5 ($\pm$ 16.3) years, height 1.59 ($\pm$ 0.09) meters, weight 51.6 ($\pm$ 8.2) kg; 36.1% were female and 100% were black. Mean ($\pm$ SD) pretreatment skin microfilarial density was 39.5 ($\pm$ 30.7), 69.6% had ≥ 20 microfilariae/mg skin and 39.7% had at least one ocular microfilaria.

Patients who were not previously exposed to ivermectin community directed treatment programs were recruited from the sub-Saharan African region (Democratic Republic of Congo, Liberia, and Ghana). Table 5 reports mean skin microfilarial density and the proportion of patients with undetectable skin microfilariae at Months 1, 6, and 12.

Table 5: Mean Microfilarial Density and Percentage of Undetectable Microfilariae in Skin of *O. volvulus* Patients (12 Years of Age and Older) at Months 1, 6, and 12 in Trial 1

Endpoint	Moxidectin N = 977	Ivermectin N = 495	Difference (95% Confidence Interval)
1 month			
Mean Microfilarial Density [‡]	0.10	2.30	-2.20 (-2.83, -1.58) p < 0.0001
% Undetectable Microfilariae [‡]	83.4%	42.9%	40.5% (35.7, 45.3) p < 0.0001

Endpoint	Moxidectin N = 977	Ivermectin N = 495	Difference (95% Confidence Interval)
6 months			
Mean Microfilarial Density	0.14	3.71	-3.57(-4.11, -3.03) p < 0.0001
% Undetectable Microfilariae [#]	91.0%	11.5%	79.6% (76.3, 82.9) p < 0.0001
12 months			
Mean Microfilarial Density	1.79	9.83	-8.04 (-9.11, -6.98) p < 0.0001
% Undetectable Microfilariae [#]	45.9%	5.4%	40.4% (36.7, 44.1) p < 0.0001

*Microfilarial density is microfilariae count/mg skin. Mean microfilarial density in skin is the average microfilarial density over skin snips from four sites.

[#]Proportion of subjects undetectable (defined as a mean skin microfilariae density of zero across all 4 skin snips).

Additionally, safety and efficacy was assessed in a smaller single ascending dose trial (Trial 2, NCT 00300768) comparing 2 mg (n = 44), 4 mg (n = 45) (2 mg and 4 mg are not approved doses) and 8 mg (n = 38) single doses of moxidectin to ivermectin. Trial 2 was conducted in Ghana in adults aged ≥ 18 to ≤ 60 years with *O. volvulus* infection. Analysis of the baseline-to-12-month change in skin microfilarial density for the proposed moxidectin 8 mg dose showed statistically significant superiority to ivermectin, p < 0.001.

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.
- Once open, the full contents of the container should be used within 24 hours with any unused content discarded.

17 PATIENT COUNSELING INFORMATION

Signs and Symptoms Associated with Microfilarial Death

Advise patients that they are likely to have flu like symptoms including malaise, myalgia, headache, tachycardia, hypotension and pruritus, most commonly during the first week after treatment.

Symptomatic Orthostatic Hypotension

Advise patients that if they feel dizzy, faint or light-headed after taking Moxidectin Tablets, they should lie down until the symptoms resolve.

Absence of Macrofilarial Activity

Advise patients that treatment with Moxidectin Tablets does not kill adult *O. volvulus* and that follow up evaluation is usually required.

Edema and Worsening of Onchodermatitis

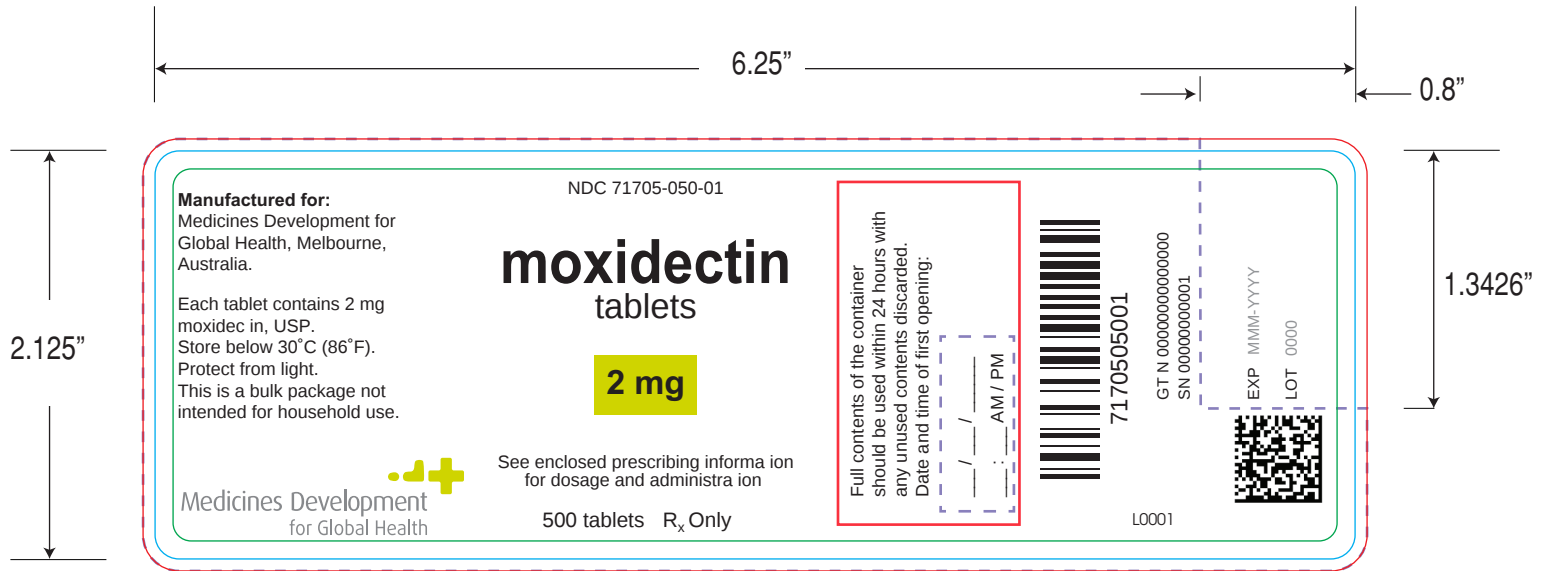
Advise patients with hyper-reactive onchodermatitis that they may be more likely to experience severe adverse reactions.

Encephalopathy in *Loa loa* Co-infected Patients

Advise patients to report any symptoms of encephalopathy to their healthcare provider.

Manufactured for: Medicines Development for Global Health, Melbourne, Victoria, Australia

© 2018 Medicines Development for Global Health. All rights reserved.



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN J FARLEY
06/13/2018