MOXIDECTIN- moxidectin tablet
Medicines Development for Global Health

HIGHLIGHTS OF PRESCRIBING INFORMATION
MOXIDECTIN tablets, for oral use

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

Initial U.S. Approval: 2018

RECENT MAJOR CHANGES

Indications and Usage (1) 2/2025
Dosage and Administration (2.1,2.2) 2/2025

INDICATIONS AND USAGE

Moxidectin is an anthelmintic indicated for the treatment of onchocerciasis due to *Onchocerca volvulus* in adults and pediatric patients aged 4 years and older and weighing at least 13 kg. (1)

Limitations of Use:

- Moxidectin Tablets do not kill adult *Onchocerca volvulus (O. volvulus)*parasites. Follow-up is advised. (1)
- The safety and efficacy of repeat administration of Moxidectin Tablets in patients with *O. volvulus*has not been studied. (1)

DOSAGE AND ADMINISTRATION

- Recommended Dosage in Adult Patients: Take 8 mg (four 2 mg tablets) as a single oral dose, with or without food. (2.1)
- Recommended Dosage in PediatricPatients (4 Years of Age and Older and Weighing at Least 13 kg):See Table below. (2.2)

Body Weight	Dose	Number of 2 mg Tablets
13 kg to less than 15 kg	4 mg	2
15 kg to less than 30 kg	6 mg	3
Greater than or equal to 30 kg	8 mg	4

DOSAGE FORMS AND STRENGTHS

Tablets: 2 mg of moxidectin. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Cutaneous,Ophthalmologicaland/or Systemic AdverseReactionsofVarying 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-InfectedPatients: 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%) in adult and pediatric patients (12 to less than 18 years of age) in Trial 1 were eosinophilia, pruritus, musculoskeletal pain, headache, lymphocytopenia, tachycardia, rash, abdominal pain, hypotension, pyrexia, leukocytosis, influenza-like illness, neutropenia, cough, diarrhea/gastroenteritis/enteritis, lymph node pain, dizziness, hyponatremia

and peripheral swelling. (6.1)
- The most common adverse reactions (incidence > 5%) in pediatric patients (4 to less than 18 years of age) in Trial 3 were abdominal pain and diarrhea. (6.1)

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.

USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding is not recommended during treatment with Moxidectin Tablets and for 7 days after treatment. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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 adult and pediatric patients aged 4 years and older and weighing at least 13 kg *[see Clinical Studies (14)]*.

Limitations of Use:

Moxidectin Tablets does not kill adult *Onchocerca volvulus (O. volvulus) parasites* . 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 inAdultPatients

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

2.2 Recommended Dosage inPediatric Patients (4 Years of Age and Older and Weighing at Least 13 kg)

The recommended dosage of Moxidectin Tablets in pediatric patients aged 4 years and older and weighing at least 13 kg is described in Table 1 below. Administer Moxidectin Tablets as a single dose taken orally with or without food [see Clinical Pharmacology *(12.3)*].

Table 1: Recommended Dosage of Moxidectin Tablets in Pediatric Patients 4 Years of Age and Older and Weighing at Least 13 kg

Body Weight	**Dose**	**Number of 2 mg Tablets**
13 kg to less than 15 kg	4 mg	2
15 kg to less than 30 kg	6 mg	3
Greater than or equal to 30 kg	8 mg	4

3 DOSAGE FORMS AND STRENGTHS

Moxidectin Tablets: 2 mg of moxidectin, white to pale yellow, uncoated, oval-shaped,

debossed on one side with “AKKA”.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cutaneous,OphthalmologicalandorSystemicAdverseReactions

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 include 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 inLoa loaCo-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 andWorseningof 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-infected Patients *[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.

Clinical Trials Experience in Adults and Pediatric Patients (12 Years to Less than 18 Years of Age)

The safety of Moxidectin Tablets was evaluated in two randomized, double-blind, active-controlled studies in patients with confirmed onchocerciasis (Trial 1 and Trial 2) *[see Clinical Studies (14)]*. In Trial 1, 978 patients (including 53 pediatric patients aged 12 to less than 18 years) received Moxidectin Tablets as a single oral dose of 8 mg and 494 patients received ivermectin (including 24 pediatric patients aged 12 to less than 18 years) as a single oral dose of approximately 150 mcg/kg. In Trial 2, 127 patients aged 18 years or older 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 aged 18 years or older 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 2. Most were related to physical, vital signs and laboratory changes associated with Mazzotti reaction *[see Warnings and Precautions (5.1)]*.

Table 2: Adverse Reactions Occurring in > 10% of Moxidectin-treated Patients with Onchocerciasis in Trial 1

Adverse Reaction	**Moxidectin N = 978**	**Ivermectin N = 494**

	n (%)	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)
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 x 10^9/L

**Neutropenia is defined as absolute neutrophil count less than 1 x 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 2above.

OtherAdverse Reactions Reported in Clinical Trials *(Trial 1 and Trial 2)*

The following adverse reactions occurred in less than 10% of subjects receiving

Moxidectin Tablets in Trial 1:

*OcularAdverse Reactions:*In Trial 1, the most common ocular adverse reactions (occurring in ≥ 0.5% of patients) is shown in Table 3.

Table 3: Ocular Adverse Reactions Occurring in ≥ 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 Trial 1 are described in Table 4.

Table 4: 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)	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)

Clinical Trials Experience in Pediatric Patients (4 Years to Less than 18 Years of Age)

The safety of Moxidectin Tablets in pediatric patients is based on data from 2 studies, Trial 1 and Trial 3 (NCT01035619).

Pediatric Patients in Trial 1

Trial 1 included 53 pediatric patients aged 12 to less than 18 years with confirmed onchocerciasis who received a single dose of Moxidectin Tablets 8 mg. Pediatric patients with confirmed infection experienced efficacy-related adverse reactions (Mazzotti reactions) such as abdominal pain, tachycardia, pyrexia, rash, peripheral swelling, and lymph node pain at a prevalence and severity similar to infected adults. Overall, the safety profile relative to age was similar across pediatric and adult patients studied in Trial 1.

Pediatric Patients in Trial 3

Trial 3 was a single-arm, open-label, age-stratified, multi-cohort, safety and pharmacokinetic trial that evaluated 36 pediatric patients aged 4 to less than 18 years with unknown O. volvulus infection status from an onchocerciasis-endemic area in Ghana. Patients were stratified by age to receive a single dose of Moxidectin Tablets as follows: aged 12 to less than 18 years received 8 mg (N = 9), 8 to less than 12 years received 8 mg (N = 9) or 6 mg (N = 9), and 4 to less than 8 years received 4 mg (N = 9). Median weight was 34.8 kg (range: 30.8 to 55.5 kg) in patients 12 to less than 18 years of age, 25.1 kg (range: 19.4 to 36.8 kg) in patients 8 to less than 12 years, and 15.6 kg (range: 13.6 to 20.6 kg) in patients 4 to less than 8 years. A majority of patients were female (58%) and 100% were black. Mazzotti reactions were not seen in this population with unknown O. volvulus infection. The most common adverse reactions in these pediatric patients were abdominal pain and diarrhea, in 3/36 (8%) patients each. No new safety signals were noted in this pediatric patient population that were not already noted in Trial 1.

7 DRUG INTERACTIONS

7.1 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

Available data from clinical trials 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 was not associated with significant embryo-fetal developmental effects at doses of approximately 15 times the recommended human dose based on body surface area (BSA) comparison. When moxidectin was dosed orally to pregnant rabbits during the period of organogenesis, no embryo-fetal developmental effects were observed at oral doses of moxidectin up to 24 times the recommended human dose based on BSA comparison *(see*Data *)*.

Daily administration of moxidectin by oral gavage to maternal female rats during organogenesis and through lactation was associated with decreased survival, adverse clinical signs, and decreased body weights in first-generation offspring during the lactation period at a moxidectin dose less than 2-times the recommended human dose based on BSA comparison. Additional findings in first-generation offspring at the same dose included delays in pinna unfolding, eye opening, and vaginal opening. Other parameters, including reproduction and neurological development in first-generation offspring were not affected at any moxidectin dose *(see*Data *)*.

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 BSA 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 BSA comparison). In the rabbit, daily oral administration of moxidectin at ≥ 5 mg/kg/day from GD 7 to GD 19 was not associated with fetal weight loss or malformations but resulted in significantly decreased maternal food consumption and body weight gains. The NOAEL values 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 BSA comparison).

In a pre-postnatal study, moxidectin doses of 0.2 and 0.5 mg/kg/day were administered by oral gavage to maternal female rats from GD 6 throughout the lactation period until LD 21. A third dose group that received maternal doses of 1.5 mg/kg/day moxidectin

(less than 2-times the recommended human dose based on BSA comparison) was divided into two cohorts with Cohort 1 receiving maternal doses from GD 6 until LD 10 and Cohort 2 receiving maternal doses from GD 6 until each individual animal littered, but not during the lactation period. First-generation offspring in Cohort 1 had adverse clinical signs (small body size, thin, weak, subdued/sluggish, pale, cold to touch, respiratory distress, blue coloration and/or no visible milk in stomach) and decreased survival and body weights during the lactation period. However, first-generation offspring in Cohort 2 did not experience adverse clinical signs, body weight loss, or reduced survival suggesting moxidectin in lactation milk was responsible for the adverse effects in offspring in Cohort 1. Additional findings included delays in pinna unfolding and eye opening in male and female offspring in both cohorts and delay of vaginal opening in female offspring in Cohort 2. No adverse effects were noted in offspring at a maternal dose of 0.5 mg/kg/day (approximately 0.6 times the recommended human dose based on BSA comparison). Reproductive performance based on mating and fertility indices and neurological development were not affected in male and female first-generation offspring at any of the administered moxidectin doses.

In another 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 BSA comparison). However, at moxidectin doses ≥ 1.1 mg/kg/day (approximately equivalent to 1.3 times the recommended human dose based on BSA 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 BSA 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. In a pre-postnatal study in rats, oral gavage administration of moxidectin at a dose less than 2-times the recommended human dose based on BSA comparison during the lactation period resulted in adverse clinical signs, weight loss, and increased mortality in rat pups suggesting moxidectin in lactation milk was responsible for the adverse effects *[seeUse in Specific Populations (8.1), andData]*.

Because of serious findings from the rat pre-postnatal study including weight loss and death, advise women that breastfeeding is not recommended at the time of treatment with Moxidectin Tablets and for 7 days after treatment.

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 (± SD) exposure ratio of moxidectin present in human breast milk to that of human plasma was approximately 1.77 mg(± 0.66) over a collection period of

28 days. The estimated mean (± SD) total infant dose, assuming the infants would consume all the breast milk collected during the study, was 0.056 mg (± 0.024 mg), which would be approximately 0.70% (± 0.30%) of the maternal dose. Relative infant dose was estimated to be 8.73% (± 0.024 mg). 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 for the treatment of onchocerciasis due to *O. volvulus* have been established in pediatric patients aged 4 years and older and weighing at least 13 kg. Use of Moxidectin Tablets for this indication is supported by evidence from adequate and well controlled studies in adult and pediatric patients aged 12 years and older with additional pharmacokinetics (PK) and safety data in pediatric patients aged 4 years and older *[see Adverse Reactions (6.1),Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

The safety and effectiveness of Moxidectin Tablets in pediatric patients younger than 4 years of age or weighing less than 13 kg 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 *[seeClinical Studies (14) andClinical 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:

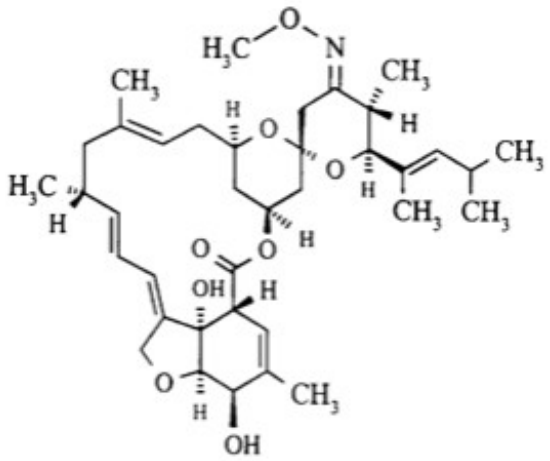


Figure 1: Moxidectin Structure

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 *[seeMicrobiology(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 5. 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 5: Mean (± 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	HealthySubjects (N =27)	Patients with Onchocerciasis (N = 31)
C_{max}(ng/mL)	58.9 ± 12.5	63.1 ± 20.0
T_{max}*(hours)	4 (2, 8)	4 (1, 4)
AUC_{inf}(ng•h/mL)	3387 ± 1328	2738 ± 1606
Half-life (hours)	784 ± 347	559 ± 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 ± SD volume of distribution of moxidectin is 2421 ± 1658 L in patients with onchocerciasis. The plasma protein binding in humans is 99.92%.

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 ± SD total clearance of moxidectin is approximately 3.50 ± 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 negligible renal elimination of moxidectin, 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.

Pediatric Patients

A pharmacokinetic study was conducted in 36 pediatric patients aged 4 to 17 years with unknown O. volvulus infection status who were administered a single dose of moxidectin (4, 6, or 8 mg). Body weight was identified as a key covariate in the population pharmacokinetic analysis. The simulated mean pharmacokinetic parameters of moxidectin following a single 4, 6, and 8 mg oral dose of Moxidectin Tablets in a U.S. pediatric population weighing 13 kg to less than 15 kg, 15 kg to less than 30 kg, and 30 kg and greater, respectively, are shown in Table 6.

Table 6: Mean (CV%) Pharmacokinetic Parameters for Moxidectin Following a Single Oral Weight Based Dose of Moxidectin Tablets in Pediatric Patients

PK Parameter	**Following 4 mg single dose in pediatric patients weighing 13 kg to less than 15 kg**	**Following 6 mg single dose in pediatric patients weighing 15 kg to less than 30 kg**	**Following 8 mg single dose in pediatric patients weighing 30 kg and greater**
C_{max}(ng/mL)	80.9 (22.3%)	90.9 (26.2%)	65.2 (30.7%)
T_{max}(hours)	3.4 (34.1%)	3.5 (34.7%)	3.5 (34.1%)
AUC_{inf}(ng•h/mL)	2388.8 (42.2%)	2840.2 (43.7%)	2660.5 (41.9%)
Half-life (hours)	299.0 (36.4%)	338.2 (41.0%)	545.8 (50.9%)

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; CV = coefficient of variation

Drug InteractionStudies

Clinical Studywith Midazolam (CYP3A4substrate)

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 in 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

Carcinogenesis

Two-year carcinogenicity studies in mice and rats were conducted with moxidectin. Mice were administered a mean dietary dose of 8.7 mg/kg/day moxidectin which is approximately equivalent to 5 times the recommended human dose based on body surface area comparison. Rats were administered a mean dietary dose of 6.1 mg/kg/day moxidectin which is approximately equivalent to 7 times the recommended human dose based on body surface area comparison. There was no evidence of tumorigenicity in either study.

Mutagenesis

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.

Impairment of Fertility

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 Toxicologyand/or Pharmacology

Moxidectin was associated with transient CNS-related clinical signs. In rats, a single oral 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 adult dogs, repeated oral 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. Similar clinical signs that were largely resolved after 24 and 48 hours in juvenile (11-week-old) and adult (10-monthold) dogs, respectively, were observed after a single oral dose of 3 mg/kg moxidectin (respectively, approximately 34 and 50 times the maximum recommended human dose in patients with onchocerciasis based on plasma AUC comparison).

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 pediatric patients ≥ 12 years with a body weight ≥ 30 kg and ≥ 10 microfilariae/mg skin. Mean (± SD) age was 42.5 (± 16.3) years, height 1.59 (± 0.09) meters, weight 51.6 (± 8.2) kg; 36.1% were female and 100% were black. Mean (± SD) pretreatment skin microfilarial density was 39.5 (± 30.7) microfilariae/mg skin, 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 7 reports mean skin microfilarial density and the proportion of patients with undetectable skin microfilariae at Months 1, 6, and 12.

Table 7: Mean Microfilarial Density and Percentage of Undetectable Microfilariae in Skin of O. volvulus Adult and Pediatric 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 [a]	0.10	2.30	-2.20 (-2.83, -1.58) p < 0.0001
% Undetectable Microfilariae [b]	83.4%	42.9%	40.5% (35.7, 45.3) p < 0.0001

6 months			
Mean Microfilarial Density [a]	0.14	3.71	-3.57(-4.11, -3.03) p < 0.0001
% Undetectable Microfilariae [b]	91.0%	11.5%	79.6% (76.3, 82.9) p < 0.0001
12 months			
Mean Microfilarial Density [a]	1.79	9.83	-8.04 (-9.11, -6.98) p < 0.0001
% Undetectable Microfilariae [b]	45.9%	5.4%	40.4% (36.7, 44.1) p < 0.0001

[a] Mean microfilarial density in skin is the average microfilarial density (microfilariae count/mg skin) over skin snips from four sites.

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

Additionally, safety and efficacy were 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 rayon coil.

Store below 30°C (86°F).

- Protect from light.
- Once open, the full contents of the container should be used within 24 hours and discard any unused content.

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. *[see Warnings and Precautions (5.1)]*.

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. *[see Warnings and Precautions (5.2)]*.

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.

Edemaand Worseningof Onchodermatitis

Advise patients with hyper-reactive onchodermatitis that they may be more likely to experience severe adverse reactions. *[see Warnings and Precautions (5.4)]*.

Encephalopathy in*Loa loa* Co-infected Patients

Advise patients to report any symptoms of encephalopathy to their healthcare provider. *[see Warnings and Precautions (5.3)]*.

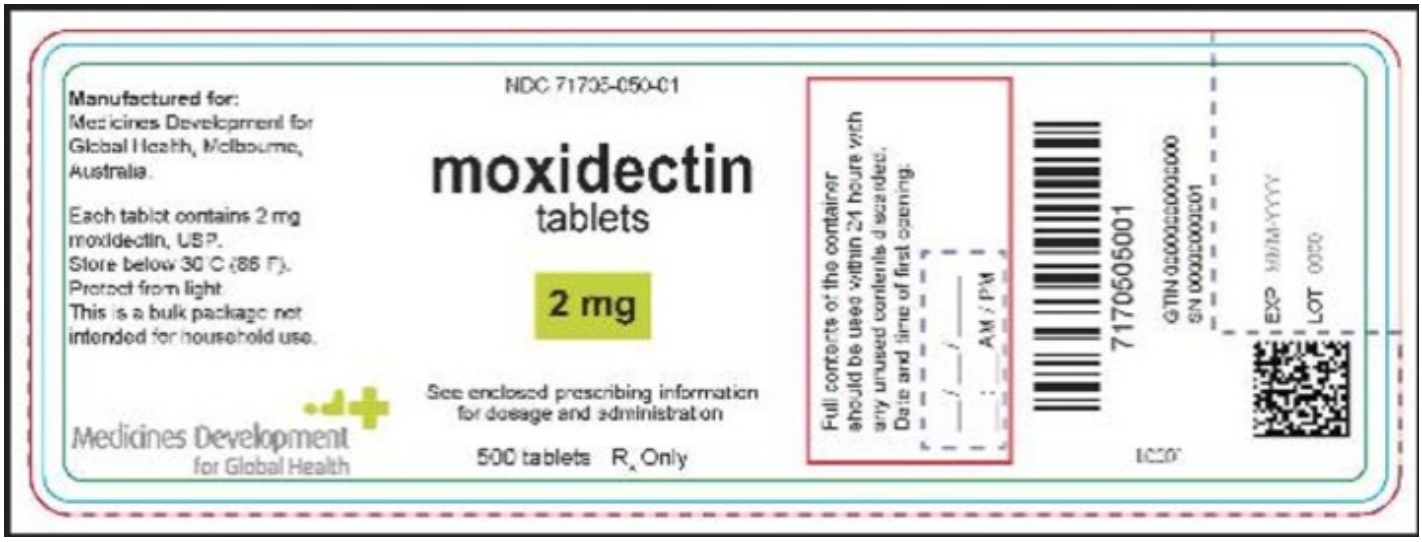
Lactation

Advise women that breastfeeding is not recommended at the time of treatment with Moxidectin Tablets and for 7 days after treatment. *[see Use in Specific Populations (8.2)]*.

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

PRINCIPAL DISPLAY PANEL

NDC 71705-050-01
moxidectin
tablets
2 mg
500 tablets
Rx Only



MOXIDECTIN moxidectin tablet			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:71705-050

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MOXIDECTIN (UNII: NGU5H31YO9) (MOXIDECTIN - UNII:NGU5H31YO9)	MOXIDECTIN	2 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	

Product Characteristics

Color	white (White to pale yellow)	**Score**	no score
Shape	OVAL	**Size**	8mm
Flavor		**Imprint Code**	AKKA
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:71705-050-01	500 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	12/02/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA210867	12/02/2019	

Labeler - Medicines Development for Global Health (754191398)

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