

## **Investigator's Brochure**

### **Ivermectin Tablets USP, 3 mg**

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## TABLE OF ABBREVIATIONS AND DEFINITIONS OF TERMS

|                  |                                                 |
|------------------|-------------------------------------------------|
| AE(s)            | Adverse event(s)                                |
| ANDA             | Abbreviated New Drug Application                |
| AUC              | Area under the concentration-time curve         |
| BE               | Bioequivalent                                   |
| C <sub>max</sub> | Maximum plasma concentration                    |
| CNS              | Central nervous system                          |
| COVID-19         | Coronavirus disease of 2019                     |
| DEC              | Diethylcarbamazine citrate                      |
| DNA              | Deoxyribonucleic acid                           |
| DP               | Dihydroartemisinin-piperaquine                  |
| FDA              | Food and Drug Administration                    |
| GABA             | Gamma-aminobutyric acid                         |
| gd               | Gestational day                                 |
| GLP              | Good laboratory practice                        |
| HED              | Human equivalent dose                           |
| HIV-1            | Human Immunodeficiency Virus-1                  |
| LD50             | Median lethal dose                              |
| LLOQ             | Lower limit of quantification                   |
| mg               | Milligram(s)                                    |
| NDA              | New Drug Application                            |
| NOAEL            | No-observed-adverse-effect-level                |
| PCR              | Polymerase chain reaction                       |
| PD               | Pharmacodynamics                                |
| PK               | Pharmacokinetics                                |
| ppb              | Parts per billion                               |
| RNA              | Ribonucleic acid                                |
| SAE              | Serious adverse event                           |
| SARS-CoV-2       | Severe Acute Respiratory Syndrome Coronavirus 2 |
| SBA              | Summary Basis of Approval                       |
| t <sub>1/2</sub> | Half-life                                       |
| T <sub>max</sub> | Time to maximum plasma concentration            |
| UK               | United Kingdom                                  |
| US               | United States                                   |
| WHO              | World Health Organization                       |
| µg               | Microgram(s)                                    |

## **1. SUMMARY**

Ivermectin is a broad-spectrum antiparasitic agent that binds selectively, and with high affinity, to glutamate-gated chloride ion channels. Binding to these sites increases cell membrane permeability to chloride ions, hyperpolarizing the nerve cell or muscle, and results in paralysis and death of the parasite. Ivermectin may also interact with other ligand-gated ion channels, such as those gated by gamma-aminobutyric acid (GABA). The selective activity of this class of compounds is attributable to the fact that some mammals do not have glutamate-gated chloride channels and that the avermectins have a low affinity for mammalian ligand-gated chloride channels. In addition, ivermectin does not readily cross the blood-brain barrier in humans ([Edenbridge, 2014](#)).

Ivermectin is an approved drug being further studied for the treatment of COVID-19, which is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus. None of the approved indications for ivermectin are related to COVID-19 or address antiviral activity as a mechanism of action, but published literature shows potential efficacy.

### **1.1. Physical, Chemical, and Pharmaceutical Properties**

#### **1.1.1. Drug Substance**

Ivermectin is a semisynthetic, anthelmintic agent for oral administration. Ivermectin is derived from the avermectins, a class of highly active broad-spectrum, anti-parasitic agents isolated from the fermentation products of *Streptomyces avermitilis*. Ivermectin is a mixture containing at least 90% 5-O-demethyl-22,23-dihydroavermectin A<sub>1a</sub> and less than 10% 5-O-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl) avermectin A<sub>1a</sub>, generally referred to as 22,23-dihydroavermectin B<sub>1a</sub> and B<sub>1b</sub>, or H<sub>2</sub>B<sub>1a</sub> and H<sub>2</sub>B<sub>1b</sub>, respectively. The respective empirical formulas are C<sub>48</sub>H<sub>74</sub>O<sub>14</sub> and C<sub>47</sub>H<sub>72</sub>O<sub>14</sub>, with molecular weights of 875.10 and 861.07, respectively ([Edenbridge, 2014](#)).

#### **1.1.2. Drug Product**

The drug product is a tablet for oral administration. Each tablet contains 3 mg ivermectin.

The drug product will be supplied in unit dose packages of 20 tablets and will be stored according to the product labeling (refer to the product labeling in the [Appendix](#)).

### **1.2. Nonclinical Information**

#### **1.2.1. Pharmacodynamics**

Ivermectin has been demonstrated to have broad spectrum anti-replicative effects on several viruses *in vitro*, including SARS-CoV-2 ([Caly et al., 2020](#)), and to reduce the viral infection rate and viral load in mosquitoes infected with dengue virus ([Xu et al., 2018](#)).

### **1.2.2. Toxicology**

Extensive nonclinical toxicology information is available from studies conducted for approved oral (FDA, 1996; Merck, 2009; Merck Sharp & Dohme, 2014; Merck Sharp & Dohme BV, 2015) and topical (Galderma Laboratories, 2018) products. These studies include the following:

- Single-dose oral toxicology conducted in mice, rats, dogs, cattle, and monkeys;
- Repeat-dose oral toxicology, including chronic toxicology, conducted in rats, rabbits, dogs, and monkeys;
- Genotoxicity;
- 2-year oral carcinogenicity in rats; and
- Developmental and reproductive toxicity in rats, mice, and rabbits.

### **1.3. Clinical Information**

#### **1.3.1. Efficacy – COVID-19**

A study conducted in Vero-hSLAM cells, a non-human primate cell line known to be susceptible to SARS-CoV-2, found that a single treatment with ivermectin reduced SARS-CoV-2 viral RNA within a 48-hour period (Caly et al., 2020).

As discussed in Section 4.2 below, in a preclinical study conducted in golden hamsters, ivermectin (400 mcg/kg) administered subcutaneously at the time of infection, prevented clinical deterioration and greatly reduced olfactory deficit.

A randomized controlled Phase III clinical trial, *A Phase III Trial to Promote Recovery From Covid 19 With Combined Doxycycline and Ivermectin Along Standard Care* (NCT04523831), was completed in September 2020. The trial was designed to evaluate the effects of potential treatments in hospitalized and outpatients with mild to moderate COVID-19 infection, from 1 June 2020 to 30 August 2020 in the largest COVID-19 dedicated hospital, Dhaka Medical College Hospital in Bangladesh. The results of this study show that patients given a combination of ivermectin (12mg stat) and doxycycline (100mg twice daily for 5 days) fared better than patients given the standard of care (acetaminophen, vitamin D, oxygen if indicated, low molecular weight heparin, and dexamethasone if indicated).

In a pilot, randomized, double-blind, placebo-controlled trial to determine the efficacy of a single dose of ivermectin (dosed at 400 µg/kg), one trial found that there was no difference in the proportion of PCR test positives among patients with mild COVID-19 and no risk factors for disease who received ivermectin versus patients who did not (Chaccour et al., 2020). There was, however, a marked reduction of anosmia/hyposmia, a reduction of cough, and a tendency to lower viral loads and lower IgG titers (Chaccour et al., 2020).

In a pilot, randomized, controlled, open-label, multicenter trial, investigators examined the antiviral activity of ivermectin in COVID-19 patients. The study compared standard of care

with and without ivermectin at 600 µg/kg/day for 5 days (Krolewiecki et al., 2020). While there was no difference in viral load reduction between groups, there was a significant difference in reduction of viral load in patients with higher median plasma ivermectin levels, and there was a positive correlation between ivermectin plasma concentration levels and viral decay rate (Krolewiecki et al., 2020).

### 1.3.2. Safety

The safety profile has been well characterized by studies conducted for approved ivermectin products and studies in the literature. Safety has been established in adults and children ≥ 15kg. The safety in children < 15 kg has not been well studied.

Single doses up to 200 µg/kg are approved in the United States (US) and Australia, and doses of up to 400 µg/kg are approved in France and the Netherlands. Multiple studies in the literature contain safety data on subjects receiving higher doses of ivermectin. The extent of exposure includes 11,893 subjects receiving at least one dose of 300 µg/kg, 11,839 subjects receiving 400 µg/kg, 541 patients receiving 600 µg/kg, and 339 patients receiving 600 µg/kg. Twelve patients each were exposed to single doses of 1500 µg/kg and 2000 µg/kg. Pediatric (≥ 15 kg) exposure to high-dose ivermectin includes 2 studies in which 398 patients received a 400 µg/kg dose and 52 subjects received a 200–400 µg/kg dose.

## 2. INTRODUCTION

### 2.1. Regulatory Status

**Chemical Name:** Ivermectin

Ivermectin is a member of the avermectin class of broad-spectrum antiparasitic agents that have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels that occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite (Edenbridge, 2014).

Within the United States, there are 3 approved New Drug Application (NDA) products containing ivermectin and 1 approved Abbreviated New Drug Application (ANDA) for each of the NDA products containing ivermectin. These products are listed in Table 1. On 27 October 2020, FDA approved ivermectin lotion to be used over-the-counter (OTC) in a prescription-to-OTC switch.

**Table 1 Ivermectin-containing Products Listed in the FDA's Orange Book**

| Application Number; Approval Date | Proprietary Name; Sponsor               | Route; Dosage Form | Strength | Indication                                                            |
|-----------------------------------|-----------------------------------------|--------------------|----------|-----------------------------------------------------------------------|
| NDA 050742; 8 Oct 1998            | Stromectol®; Merck Sharp and Dohme Corp | Oral; Tablet       | 3 mg     | • treatment of intestinal (ie, non-disseminated) strongyloidiasis due |

|                             |                                                       |                    |      |                                                                                                                                               |
|-----------------------------|-------------------------------------------------------|--------------------|------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| ANDA 204154;<br>24 Oct 2014 | Ivermectin;<br>Edenbridge<br>Pharmaceuticals,<br>LLC  |                    |      | to the nematode parasite<br>Strongyloides stercoralis<br>• treatment of onchocerciasis due to<br>the nematode parasite Onchocerca<br>volvulus |
| NDA 202736;<br>7 Feb 2012   | Sklice®; Arbor<br>Pharmaceuticals<br>LLC              | Topical;<br>Lotion | 0.5% | • treatment of head lice infestations in<br>patients 6 months of age and older                                                                |
| ANDA 210720<br>6 May 2020   | Ivermectin; Taro<br>Pharmaceutical<br>Industries Ltd. |                    |      |                                                                                                                                               |
| NDA 206255;<br>19 Dec 2014  | Soolantra™;<br>Galderma<br>Laboratories LP            | Topical,<br>Cream  | 1%   | • treatment of inflammatory lesions<br>of rosacea                                                                                             |
| ANDA 210019<br>13 Sept 2019 | Ivermectin; Teva<br>Pharmaceuticals<br>USA, Inc       |                    |      |                                                                                                                                               |

ANDA = Abbreviated New Drug Application; FDA = Food and Drug Administration; NDA = New Drug Application

Source: FDA's Orange Book; accessed on 11 January 2021

None of the products are approved for an indication related to COVID-19 or address antiviral activity as a mechanism of action. Oral ivermectin (Stromectol) is also marketed worldwide; a list of ivermectin products, approved indications, and dosing regimens are shown in [Table 2](#).

**Table 2 Approved Dosage Regimens for Oral Ivermectin by Regulatory Region**

| <b>Regulatory Approval Region</b> | <b>Proprietary Name; Sponsor</b>                                   | <b>Indication/s</b>                                                                                                                                                                                      | <b>Dosage Regimen</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Australia                         | Stromectol, 3 mg Tablet; Merck Sharp & Dohme (Australia) Pty. Ltd. | Onchocerciasis                                                                                                                                                                                           | Approx. 200 µg ivermectin/kg body weight. The suggested dose interval for most patients is 12 months. At some sites, it may be preferable to use a 6-month interval, depending on such considerations as density of skin microfilariae and/or prevalence.                                                                                                                                                                                                                          |
|                                   |                                                                    | Intestinal strongyloidiasis (anguillulosis)                                                                                                                                                              | Approx. 150 µg ivermectin/kg body weight. The suggested dose interval for most patients is 12 months. At some sites, it may be preferable to use a 6-month interval, depending on such considerations as density of skin microfilariae and/or prevalence.                                                                                                                                                                                                                          |
|                                   |                                                                    | <ul style="list-style-type: none"> <li>• Crusted scabies in conjunction with topical therapy</li> <li>• Human sarcoptic scabies when prior topical treatment has failed or is contraindicated</li> </ul> | <p>Approximately 200 µg ivermectin/kg body weight per dose.</p> <ul style="list-style-type: none"> <li>• Classic/typical scabies: 2 doses (1 dose on day 1 and another dose between day 8 and day 15).</li> <li>• Crusted scabies: <ul style="list-style-type: none"> <li>○ Mild cases: 2 doses (1 dose on day 1 and another dose between day 8 and day 15)</li> <li>○ Moderate to severe cases: More than 3 doses may be required for effective treatment.</li> </ul> </li> </ul> |
| France;<br>The Netherlands        | Stromectol, 3 mg Tablet; Merck Sharp & Dohme BV                    | Intestinal strongyloidiasis (anguillulosis)                                                                                                                                                              | Single dose of 200 µg of ivermectin per kg body weight.                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                   |                                                                    | Microfilaremia in patients with lymphatic filariasis caused by Wuchereria bancrofti                                                                                                                      | Approximately 150 to 200 µg/kg of body weight every 6 months. If treatment can only be administered every 12 months, the dosage is 300 to 400 µg/kg of body weight                                                                                                                                                                                                                                                                                                                 |
|                                   |                                                                    | Human sarcoptic scabies                                                                                                                                                                                  | <p>Single dose of 200 µg/kg of body weight.</p> <ul style="list-style-type: none"> <li>• Common scabies: A second dose may be administered within 2 weeks if new lesions or positive parasitology examination.</li> <li>• Profuse and crusting scabies: a second dose within 8 to 15 days may be necessary</li> </ul>                                                                                                                                                              |

**Table 2 Approved Dosage Regimens for Oral Ivermectin by Regulatory Region**

| Regulatory Approval Region | Proprietary Name; Sponsor                 | Indication/s                             | Dosage Regimen                                                                                                                                                                                                                                                             |
|----------------------------|-------------------------------------------|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| United States              | Stromectol, 3 mg tablet; Merck & Co., Inc | Strongyloidiasis of the intestinal tract | Single dose of 200 µg/kg of body weight. In general, additional doses are not necessary                                                                                                                                                                                    |
|                            |                                           | Onchocerciasis                           | Single dose of 200 µg/kg of body weight. In mass distribution campaigns in international treatment programs, the most commonly used dose interval is 12 months. For the treatment of individual patients, retreatment may be considered at intervals as short as 3 months. |

Source: Oral ivermectin product labels approved by regulatory authorities available in the English language.

## 2.2. Rationale

COVID-19 is a serious global health threat. The causative agent has been identified as SARS-CoV-2. On 30 January 2020, the WHO declared the outbreak a Public Health Emergency of International Concern, and on 11 March 2020, the WHO characterized COVID-19 as a pandemic.

SARS-CoV-2 belongs to a family of coronaviruses that may cause various symptoms such as pneumonia, fever, breathing difficulty, and lung infection. These viruses are common in animals worldwide, but very few cases have been known to affect humans ([Adhikari et al., 2020](#)). To date, most SARS-CoV-2 infected patients have developed mild symptoms such as dry cough, sore throat, and fever. The majority of cases have spontaneously resolved. However, some have developed various fatal complications including organ failure, septic shock, pulmonary edema, severe pneumonia, and acute respiratory distress syndrome ([Sohrabi et al., 2020](#)). To date, only Veklury (remdesivir), an injectable medication administered in a hospital or other healthcare setting capable of providing acute care comparable to inpatient care, has been approved for the treatment of COVID-19. No outpatient therapies have been approved for the treatment of COVID-19.

Ivermectin has been shown to have broad spectrum antiviral activity against several RNA viruses *in vitro*, including human immunodeficiency virus-1 (HIV-1), dengue virus, West Nile Virus, Venezuelan equine encephalitis virus, and influenza ([Wagstaff et al., 2012](#)); ([Mastrangelo et al., 2012](#)); ([Gotz et al., 2016](#)), and against the DNA virus pseudorabies virus both *in vitro* and *in vivo* ([Lv et al., 2018](#)). Ivermectin has been shown to inhibit the interaction between the HIV-1 integrase protein and the importin  $\alpha/\beta 1$  heterodimer responsible for integrase protein nuclear import, and subsequently to inhibit HIV-1 replication ([Wagstaff et al., 2012](#)). The use of importin  $\alpha/\beta 1$  during infection by many RNA viruses is believed to account in part for the broad spectrum antiviral activity of ivermectin ([Yang et al., 2020](#)). Similar disruption of a nuclear localization signal by ivermectin was identified for the DNA-based pseudorabies virus ([Lv et al., 2018](#)).

As discussed above in [Section 1.3.1](#), potential efficacy of ivermectin has been shown *in vitro* and in various preclinical and clinical trials.

### 2.3. Therapeutic Indications

Ivermectin is being investigated for the treatment of COVID-19 in patients aged 18 and over with certain comorbidities, or with shortness of breath as part of their COVID-19 illness, and those aged 65 and over, with confirmed or possible COVID-19, and who are well enough to remain in the community. Onset of symptoms or a positive test for SARS-Co-V2 infection with symptoms of COVID-19 must be within the last 14 days.

Oral ivermectin is currently approved for the indications shown in [Table 3](#).

**Table 3 Approved Indications for Oral Ivermectin**

| Indication                                                                                 | Countries                                                                                                                  |
|--------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Onchocerciasis                                                                             | <ul style="list-style-type: none"><li>• Australia</li><li>• France</li><li>• United States</li></ul>                       |
| Intestinal strongyloidiasis (anguillulosis)                                                | <ul style="list-style-type: none"><li>• Australia</li><li>• France</li><li>• Netherlands</li><li>• United States</li></ul> |
| Crusted scabies in conjunction with topical therapy                                        | <ul style="list-style-type: none"><li>• Australia</li></ul>                                                                |
| Human sarcoptic scabies                                                                    | <ul style="list-style-type: none"><li>• Australia</li><li>• France</li><li>• Netherlands</li></ul>                         |
| Microfilaremia in patients with lymphatic filariasis caused by <i>Wuchereria bancrofti</i> | <ul style="list-style-type: none"><li>• France</li><li>• Netherlands</li></ul>                                             |

### 2.4. General Investigational Approach

The effect of ivermectin will be tested in patients aged 18 and over with certain comorbidities, or with shortness of breath as part of their COVID-19 illness, and those aged 65 and over, with confirmed or possible COVID-19 who meet the current case definition for possible COVID-19, and who are well enough to remain in the community. Onset of symptoms or a positive test for SARS-Co-V2 infection with symptoms of COVID-19 must be within the last 14 days. The PRINCIPLE trial is an open, prospective, individually randomised, platform, response adaptive, controlled clinical trial in community care in the UK. The trial will test an oral dose of 300 µg/kg body weight for 3 days plus usual care compared to usual care alone (usual care will follow current NHS care provision).

## Physical, Chemical, and Pharmaceutical Properties and Formulation

### 3.1 Drug Substance

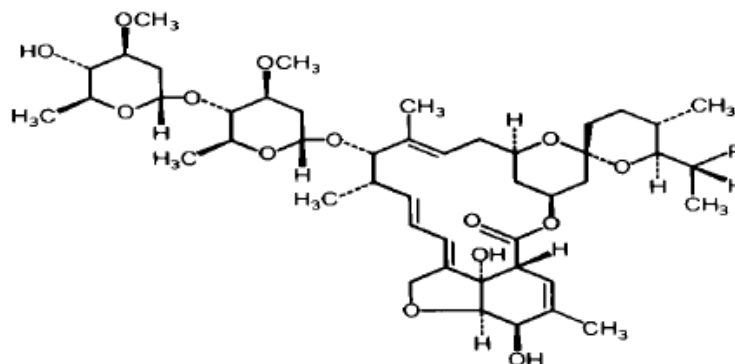
The following information for ivermectin drug substance (*italicized*) is provided in the drug product labeling from Edenbridge Pharmaceuticals, LLC ([Edenbridge, 2014](#)) and is applicable to all approved ivermectin products:

*Ivermectin is a semisynthetic, anthelmintic agent for oral administration. Ivermectin is derived from the avermectins, a class of highly active broad-spectrum, anti-parasitic agents isolated from the fermentation products of Streptomyces avermitilis. Ivermectin is a mixture containing at least 90% 5-O-demethyl-22,23-dihydroavermectin A<sub>1a</sub> and less than 10% 5-O-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl) avermectin A<sub>1a</sub>, generally referred to as 22,23-dihydroavermectin B<sub>1a</sub> and B<sub>1b</sub>, or H<sub>2</sub>B<sub>1a</sub> and H<sub>2</sub>B<sub>1b</sub>, respectively. The respective empirical formulas are C<sub>48</sub>H<sub>74</sub>O<sub>14</sub> and C<sub>47</sub>H<sub>72</sub>O<sub>14</sub>, with molecular weights of 875.10 and 861.07, respectively.*

*Ivermectin is a white to yellowish-white, nonhygroscopic, crystalline powder with a melting point of about 155°C. It is insoluble in water but is freely soluble in methanol and soluble in 95% ethanol.*

The chemical structure and formula for ivermectin are provided in [Figure 1](#).

**Figure 1 Structure and Formulas for Ivermectin**



**Component B<sub>1a</sub>, R = C<sub>2</sub>H<sub>5</sub>**

**Component B<sub>1b</sub>, R = CH<sub>3</sub>**

|                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemical Name:    | <u>B<sub>1a</sub></u> : Avermectin A <sub>1a</sub> , 5- <i>O</i> -demethyl-22,23-dihydro-<br>(2 <i>aE</i> ,4 <i>E</i> ,8 <i>E</i> )-5'- <i>S</i> ,6 <i>S</i> ,6'- <i>R</i> ,7 <i>S</i> ,11 <i>R</i> ,13 <i>R</i> ,15 <i>S</i> ,17 <i>aR</i> ,20 <i>R</i> ,20 <i>aR</i> ,20 <i>bS</i> )-6'- <i>(S)</i> - <i>sec</i> -<br>Butyl-3',4',5',6,6',7,10,11,14,15,17 <i>a</i> ,20,20 <i>a</i> ,20 <i>b</i> -tetradecahydro-20,20 <i>b</i> -<br>dihydroxy[11,15-methano-2 <i>H</i> ,13 <i>H</i> ,17 <i>H</i> -furo[4,3,2-<br><i>pq</i> ][2,6]benzodioxacyclooctadecin-13,2'-[2 <i>H</i> ]pyran]-7-yl 2,6dideoxy-4- <i>O</i> -(2,6-<br>dideoxy-3- <i>O</i> -methyl- $\alpha$ -L- <i>arabino</i> -hexopyranosyl)-3- <i>O</i> -methyl- $\alpha$ -L- <i>arabino</i> -<br>hexopyranoside<br><u>B<sub>1b</sub></u> : Avermectin A <sub>1a</sub> , 5- <i>O</i> -demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-<br>(1-methylethyl)-<br>2 <i>aE</i> ,4 <i>E</i> ,8 <i>E</i> )-5'- <i>S</i> ,6 <i>S</i> ,6'- <i>R</i> ,7 <i>S</i> ,11 <i>R</i> ,13 <i>R</i> ,15 <i>S</i> ,17 <i>aR</i> ,20 <i>R</i> ,20 <i>aR</i> ,20 <i>bS</i> )-<br>3',4',5',6,6',7,10,11,-oxospirol[11,15-methano-2 <i>H</i> ,13 <i>H</i> ,17 <i>H</i> -furo[4,3,2-<br><i>pq</i> ][2,6]benzodioxacyclooctadecin-13,2'-[2 <i>H</i> ]pyran]-7-yl 2,6dideoxy-4- <i>O</i> -(2,6-<br>dideoxy-3- <i>O</i> -methyl- $\alpha$ -L- <i>arabino</i> -hexopyranosyl)-3- <i>O</i> -methyl- $\alpha$ -L- <i>arabino</i> -<br>hexopyranoside |
| Formula:          | <u>B<sub>1a</sub></u> : C <sub>48</sub> H <sub>74</sub> O <sub>14</sub><br><u>B<sub>1b</sub></u> : C <sub>47</sub> H <sub>72</sub> O <sub>14</sub>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Molecular Weight: | <u>B<sub>1a</sub></u> : 875.10<br><u>B<sub>1b</sub></u> : 861.07                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| CASRN:            | 70288-86-7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Source:           | Current USP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

## 3.2 Drug Product

### 3.2.1 Description

The drug product will be supplied from Edenbridge Pharmaceuticals, LLC pursuant to ANDA 204154. The drug product is on the WHO Prequalification List (WHO Reference Number NT009 (a)). The drug product labeling is in the [Appendix](#).

### 3.2.2 Storage, Stability, and Handling

Ivermectin storage, stability, and handling are as described in the drug product labeling in the [Appendix](#).

## **4. NONCLINICAL STUDIES**

### **4.1. Nonclinical Pharmacology**

#### **4.1.1. Overview of Nonclinical Pharmacology Studies**

Information related to mechanism of action, nonclinical efficacy, pharmacokinetics (PK) and product metabolism in animals, and toxicology information available for ivermectin is derived from: (i) published scientific literature; (ii) the approved labeling for Stromectol, Ivermectin Tablets (Edenbridge Pharmaceuticals, LLC), and Soolantra; and (iii) the associated studies performed for approval of the aforementioned products, as summarized in their respective Summary Basis of Approval (SBA), if applicable. The primary points related to ivermectin oral tablets nonclinical safety are summarized below:

- Ivermectin is a broad-spectrum antiparasitic agent that binds glutamate-gated chloride ion channels to paralyze and kill parasites. Ivermectin may also interact with other ligand-gated chloride channels; its selectivity is attributable to its low affinity to mammalian ligand-gated ion channels and its inability to cross the blood brain barrier (see Section 4.1.2).
- Ivermectin prevents nuclear transport of host and viral proteins required for replication of viruses such as HIV-1, dengue virus, and SARS-CoV-2 (see Section 4.1.2).
- Nonclinical information in the FDA-approved labeling of ivermectin products provides nonclinical information to support the safe use of the proposed product to treat patients with COVID-19 (Merck, 2009; Edenbridge, 2014; Galderma Laboratories, 2018).

#### **4.1.2. Mechanism of Action**

##### **4.1.2.1. Information From the Approved Labeling of Ivermectin Products**

The following information for ivermectin mechanism of action (*italicized*) is provided in the drug product labeling from Edenbridge Pharmaceuticals, LLC (Edenbridge, 2014) and is applicable to all approved ivermectin products:

*Ivermectin is a member of the avermectin class of broad-spectrum antiparasitic agents which have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).*

*The selective activity of compounds of this class is attributable to the facts that some mammals do not have glutamate-gated chloride channels and that the avermectins have a low affinity for mammalian ligand-gated chloride channels. In addition, ivermectin does not readily cross the blood-brain barrier in humans.*

*Ivermectin is active against various life-cycle stages of many but not all nematodes. It is active against the tissue microfilariae of Onchocerca volvulus but not against the adult form. Its activity against Strongyloides stercoralis is limited to the intestinal stages.*

#### **4.1.2.2. Information From the Published Literature**

Ivermectin has been demonstrated to be a broad-spectrum inhibitor of importin  $\alpha/\beta$  nuclear import, with no effect on a range of other nuclear import pathways, and to subsequently inhibit replication of RNA viruses that are strongly reliant on importin  $\alpha/\beta$  heterodimer nuclear import such as HIV-1 and dengue virus (Wagstaff et al., 2012).

#### **4.1.3. Efficacy Models – COVID-19**

##### **4.1.3.1. Information From Published Literature**

One study in the published literature has evaluated the antiviral efficacy of ivermectin against SARS-CoV-2 *in vitro* (Caly et al., 2020). As ivermectin is known to have anti-replication activity in several RNA viruses that rely on the importin  $\alpha/\beta$  heterodimer for nuclear import of host and viral proteins, the authors tested the effect on cells infected with SARS-CoV-2. In the study, Vero/hSLAM cells were infected with SARS-CoV-2 isolate (Australia/VIC01/2020) at a multiplicity of infection of 0.1 for 2 hours, followed by the addition of 5 mM ivermectin. Supernatant and cell pellets were harvested at days 0 - 3 and analyzed by reverse transcription polymerase chain reaction for the replication of SARS-CoV-2 RNA.

At 24 hours after ivermectin treatment, there was a 93% reduction in viral RNA present in the supernatant and a 99.8% reduction in cell-associated viral RNA of samples treated with ivermectin compared to the vehicle DMSO. By 48 hours this effect increased to an approximately 5000-fold reduction of viral RNA in ivermectin-treated compared to control samples, indicating that ivermectin treatment resulted in the effective loss of essentially all viral material by 48 and 72 hours. No toxicity of ivermectin was observed at any of the timepoints tested, in either the sample wells or in parallel-tested drug alone samples. Using serial dilutions of ivermectin, the half maximal inhibitory concentration (IC<sub>50</sub>) was determined to be approximately 2mM under these conditions (Caly et al., 2020).

#### **4.2. Preclinical**

In a preclinical study, investigators from Institut Pasteur investigated the effects of ivermectin alone on SARS-CoV-2 infection using the golden Syrian hamster model as a model for COVID-19 (Dias de Melo et al., 2020). Even though ivermectin had no effect on viral load, SARS-CoV-2-associated pathology was greatly attenuated (Dias de Melo et al., 2020). Ivermectin had a sex-dependent and compartmentalized immunomodulatory effect, preventing clinical deterioration and reducing olfactory deficit in infected animals (Dias de Melo et al., 2020). Ivermectin dramatically reduced the *Il-6/Il-10* ratio in lung tissue, which likely accounts for the more favorable clinical presentation in animals treated with ivermectin (Dias de Melo et al., 2020).

#### **4.3. Pharmacokinetics and Product Metabolism in Animals**

##### **4.3.1. Pharmacokinetic Information From the SBAs of Ivermectin Products**

MK-0933 (ivermectin) was administered orally (in sesame oil) to two groups of mice, in doses of 0.1 or 0.5 mg/kg/day for 35 days (Study TT-82-071-0). Peak plasma drug concentrations were 5 and 20 nanograms/ml, in the low- and high-dose groups, respectively. At necropsy, analysis of brain tissue revealed MK-9033 concentrations of 35 ppb in some animals (because of technical difficulties encountered in the brain assay, the value of 35 ppb may or may not be reliable) (FDA, 1996).

In an acute study in mice, a single oral dose of MK-0933 (51 mg/kg; human equivalent dose [HED] 4 mg/kg) was administered in sesame oil (Study TT-82-088-0). This dose was lethal to 4 of 30 animals, while other animals became moribund. At various times after dosing, blood was drawn from surviving animals, and some animals were sacrificed for analysis of brain tissue. The peak drug concentrations found in this study were 5000 ng/mL in plasma and 400 ppb in brain (FDA, 1996).

In another study, MK-0933 in sesame oil was administered orally by gavage to 2 groups of 4 female Beagle dogs at doses of either 0.5 or 2 mg/kg/day (HED: 0.27 or 1.08 mg/kg/day) for 35 days (Study TT-82-070-0). Peak plasma drug concentrations of 175 and 1500 ng/mL occurred during the third week of the study, but then declined during the last 2 weeks of the study. One dog in the 2 mg/kg/day group developed tremors, ataxia, and depression and was sacrificed moribund on day 24. In this animal, the drug was detected in the cerebrospinal fluid at a concentration of 3 ng/mL. In the other 7 animals sacrificed on day 35, the drug was not detected in cerebrospinal fluid (detection limit 1 ng/mL) (FDA, 1996).

#### **4.4. Toxicology**

The studies in the following sections were conducted by Merck for the approval of oral ivermectin for the strongyloidiasis and onchocerciasis indications. Single doses of 1 mg/kg (HED = 0.32 mg/kg) and repeated doses of 0.5 mg/kg (HED = 0.16 mg/kg) in rhesus monkeys were usually associated with no treatment-related effects. Higher doses were associated with emesis, tremors, ataxia, mydriasis, and sedation.

In the Stromectol SBA, it was noted that “Ivermectin appears to be neurotoxic, presumably through an effect on GABA neurons. The compound appeared to be more toxic in rodents than in subhuman primates, especially with regard to central nervous system (CNS) effects such as tremors and ataxia. In mice, effects were seen at doses as low as 0.2 mg/kg/day; in monkeys, mild toxicity (emesis) was observed following a dose of 2 mg/kg, which is 10 times higher than the recommended human dose of 200 mcg/ml. At these doses, peak plasma drug levels were 5.5 times higher in the monkeys than in humans (110 versus 20 nanograms/ml)” (FDA, 1996). A distinction should therefore be drawn between toxicity results in rodents versus nonrodents.

#### 4.4.1. Single-dose Studies

##### 4.4.1.1. Information From the SBAs of Ivermectin Products

A summary of the acute toxicity is provided in the SBA for Stromectol. This data is presented below with HED calculations added. Human equivalent doses were calculated according to the *Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* for a 60 kg adult human.

In an oral ascending-dose study conducted in 8 adult rhesus monkeys under good laboratory practice (GLP) conditions, the dose level at which no adverse effects occurred (NOAEL) was determined to be 1 mg/kg (HED = 0.32 mg/kg). Emesis was observed with a dose-related incidence at doses of 2 mg/kg (HED = 0.64 mg/kg) and higher. Mydriasis was seen at doses of 6 mg/kg (HED = 1.92 mg/kg) and above. Decreased activity and/or sedation occurred at 24 mg/kg (HED = 7.68 mg/kg). After the minimum toxic dose of 2 mg/kg, the peak plasma drug concentrations were highest at 24 hours and averaged 110 nanograms/mL. No postmortem or microscopic observations were reported for this study (FDA, 1996).

A summary of the LD<sub>50</sub> in various species is provided in Table 4. A range is provided in cases where the LD<sub>50</sub> was determined in multiple studies.

**Table 4 LD<sub>50</sub> and Human Equivalent Doses for Ivermectin**

| Species, Gender         | Route of Administration | LD <sub>50</sub> (mg/kg)  | Source                     |
|-------------------------|-------------------------|---------------------------|----------------------------|
| Mice, male              | oral                    | 11.6                      | Stromectol SBA (FDA, 1996) |
| Mice, female            | oral                    | 24.6–87.2                 | Stromectol SBA (FDA, 1996) |
| Rats, male              | oral                    | 42.8–52.8                 | Stromectol SBA (FDA, 1996) |
| Rats, female            | oral                    | 44.3–52.8                 | Stromectol SBA (FDA, 1996) |
| Rats, infant (1–2 days) | oral                    | 2.3                       | Stromectol SBA (FDA, 1996) |
| Rabbits, both sexes     | dermal                  | 406                       | Stromectol SBA (FDA, 1996) |
| Rats                    | subcutaneous            | Between 5–50 <sup>a</sup> | Dadarkar et al., 2007      |
|                         |                         | 51.5 <sup>b</sup>         |                            |

<sup>a</sup>Evaluated via “Acute Toxic Class” method as per OECD 423

<sup>b</sup>Evaluated via conventional acute toxicity test using probit analysis

SBA = Summary Basis of Approval

The signs of toxicity observed in rodents after oral administration were ptosis, bradypnea, ataxia, tremors, and loss of the righting reflex (FDA, 1996). After subcutaneous administration, post mortem lesions were observed in the form of congestion of liver, which showed centrilobar necrosis and hemorrhages upon histopathological analysis (Dadarkar et al., 2007).

A study was conducted in dogs using single oral doses of 5–80 mg/kg. Mydriasis, ataxia, and tremors occurred at 10 mg/kg (HED = 5.6 mg/kg). Two of the 4 dogs dosed at 80 mg/kg (HED = 44.4 mg/kg) became comatose and died (FDA, 1996).

In experiments with cattle, subcutaneous doses of up to 6 mg/kg were well-tolerated. However, in a group of 4 calves that received 8 mg/kg, 1 calf died, and 2 others were sacrificed moribund. The compound was thought to have caused central nervous system depression in these cattle (FDA, 1996).

#### 4.4.2. Repeat-dose Studies

##### 4.4.2.1. Information From the SBAs of Ivermectin Products

Several repeat-dose toxicity studies were conducted for the approval of Stromectol. The results of these studies are summarized in Table 5.

**Table 5 Repeat-dose Toxicity Studies for Oral Ivermectin**

| Study Type; Duration                               | Species       | Age, Number                                                    | Daily Dose Administered (mg/kg) | NOAEL (mg/kg)    | HED (mg/kg) | Treatment-related Effects                                                                                                                                                                                                                                                                                                                                                                                             |
|----------------------------------------------------|---------------|----------------------------------------------------------------|---------------------------------|------------------|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2-week toxicity, GLP                               | Rhesus monkey | Adult, 4/sex/group                                             | 0, 0.3, 0.6, 1.2                | 1.2 <sup>a</sup> | 0.38        | None                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 2-week toxicity, GLP                               | Rhesus monkey | Neonatal, 8/group (5 M, 3 F)                                   | 0, 0.04, 0.1                    | 0.1 <sup>a</sup> | 0.03        | None                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 14-week subchronic toxicity, GLP status not stated | Rat           | Adults derived from dams treated with ivermectin, 20/sex/group | 0, 0.4, 0.8, 1.6                | 0.4              | 0.06        | At higher doses: <ul style="list-style-type: none"> <li>• enlarged spleens with congestion of red pulp and extramedullary hematopoiesis</li> <li>• reactive hyperplasia of bone marrow seen in animals with enlarged spleens, suggesting possible intravascular hemolysis</li> <li>• iron-positive pigment in renal tubular epitheliums</li> <li>• hepatocellular vacuolation and pigment in Kupffer cells</li> </ul> |
| 14-week subchronic toxicity, GLP status not stated | Dog           | Adult, 4/sex/group                                             | 0, 0.5, 1, 2                    | 0.5              | 0.27        | At higher doses: <ul style="list-style-type: none"> <li>• salivation</li> <li>• mydriasis</li> <li>• anorexia</li> <li>• dehydration</li> <li>• tremors</li> <li>• ataxia</li> <li>• some animals became recumbent</li> </ul>                                                                                                                                                                                         |

**Table 5 Repeat-dose Toxicity Studies for Oral Ivermectin**

| Study Type; Duration                         | Species | Age, Number  | Daily Dose Administered (mg/kg)              | NOAEL (mg/kg) | HED (mg/kg) | Treatment-related Effects                                                                              |
|----------------------------------------------|---------|--------------|----------------------------------------------|---------------|-------------|--------------------------------------------------------------------------------------------------------|
|                                              |         |              |                                              |               |             | <ul style="list-style-type: none"> <li>4/8 dogs at 2 mg/kg sacrificed due to poor condition</li> </ul> |
| 6-month POC and PK study in rabbits, non-GLP | Rabbit  | Adults, 30 M | 1, 2, or 3 rods of extended-release implants | 3 rods        | N/A         | No major AEs attributable to drug                                                                      |

<sup>a</sup> Adverse treatment-related effects not reported at the dose levels administered.

AE = adverse event; F = female; GLP = good laboratory practice; HED = human equivalent dose; M = male; N/A = not applicable; NOAEL = no adverse effects level; PK = pharmacokinetic; POC = proof-of-concept  
Source: Stromectol SBA (FDA, 1996) and (Chaccour et al., 2015)

### Toxicity of Degradation Products Forming Upon Prolonged Storage

Two additional studies were conducted to determine the toxicity of degradation products that developed in Stromectol tablets that had been stored for 2 years. Some loss of potency (approximately 5–10%) occurred as a result of the formation of the unidentified oxidative degradation products. These 2-week toxicity studies were conducted in rats and rhesus monkeys at a dose of 0.5 mg/kg (HED [rat] = 0.08 mg/kg; HED [rhesus] = 0.16 mg/kg). In both studies, no treatment-related effects were observed.

### Chronic Toxicology

In the SBA for Soolantra (FDA, 2013), 2 chronic oral toxicity studies are described. The study findings are summarized here.

In a 27-week oral toxicity study in rats, treatment-related mortality was noted at 3 and 12 mg/kg/day. Decreased body weight gain or even weight loss was noted at 3 and 12 mg/kg/day during the first 2 weeks. It appeared that the 12 mg/kg/day dose induced significant toxicity during the first 2 weeks, especially in females, followed by a clear habituation to the toxicity and partial recovery. Histopathology findings included slight white matter vacuolation in brain and cervical spinal cord, minimal mucosal hyperplasia and minimal to slight increase of lymphoid cells in the lamina propria of cecum, and minimal decreased secretion in seminal vesicles. The NOAEL was identified as 0.1 mg/kg/day in this study.

In a 39-week oral toxicity study in Beagle dogs, mydriasis and hypersalivation were observed at 1.5 mg/kg/day. Body weight loss was observed in both males and females at 1.5 mg/kg/day during the first week of dosing. No other significant toxicity was noted. The NOAEL was identified as 0.5 mg/kg/day in this study.

#### **4.4.3. Carcinogenicity**

##### **4.4.3.1. Information From the Approved Labeling of Ivermectin Products**

The following carcinogenicity information for ivermectin (*italicized*) is provided in the Soolantra labeling ([Galderma Laboratories, 2018](#)) and is applicable to all approved ivermectin products:

*In a 2-year dermal mouse carcinogenicity study, ivermectin was administered to CD-1 mice at topical doses of 1, 3, and 10 mg/kg/day (0.1%, 0.3% and 1% ivermectin cream applied at 2 ml/kg/day). No drug-related tumors were noted in this study up to the highest dose evaluated in this study of 10 mg/kg/day.*

*In a 2-year oral rat carcinogenicity study, ivermectin was administered to Wistar rats at gavage doses of 1, 3, and 9 mg/kg/day. A statistically significant increase in the incidence of hepatocellular adenoma was noted in males treated with 9 mg/kg/day ivermectin. The clinical relevance of this finding is unknown. No drug-related tumors were noted in females up to the highest dose evaluated in this study of 9 mg/kg/day. No drug-related tumors were noted in males at doses  $\leq 3$  mg/kg/day.*

#### **4.4.4. Reproductive and Development Toxicity**

##### **4.4.4.1. Information From the Approved Labeling of Ivermectin Products**

Fertility studies (Segment I) were conducted for the approval of Stromectol and Soolantra.

The following reproductive and developmental toxicity information for ivermectin (*italicized*) is provided in the drug product labeling from Edenbridge Pharmaceuticals, LLC ([Edenbridge, 2014](#)) and is applicable to all approved ivermectin products:

*Ivermectin had no adverse effects on the fertility in rats in studies at repeated doses of up to 3 times the maximum recommended human dose of 200 mcg/kg (on a mg/m<sup>2</sup>/day basis).*

*Ivermectin has been shown to be teratogenic in mice, rats, and rabbits when given in repeated doses of 0.2, 8.1, and 4.5 times the maximum recommended human dose, respectively (on a mg/m<sup>2</sup>/day basis). Teratogenicity was characterized in the three species tested by cleft palate; clubbed forepaws were additionally observed in rabbits. These developmental effects were found only at or near doses that were maternotoxic to the pregnant female. Therefore, ivermectin does not appear to be selectively fetotoxic to the developing fetus. There are, however, no adequate and well-controlled studies in pregnant women. Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.*

The following information for ivermectin (*italicized*) is provided in the Soolantra labeling ([Galderma Laboratories, 2018](#)) and is applicable to all approved ivermectin products:

*A pre-and postnatal development study was conducted in rats. Oral doses of 1, 2 and 4 mg/kg/day ivermectin were administered to pregnant female rats during gestational days 6–20 and lactation days 2–20. Neonatal death occurred at doses  $\geq 2$  mg/kg/day. Behavior development of newborn rats was adversely affected at all doses.*

*In a fertility study, oral doses of 0.1, 1 and 9 mg/kg/day ivermectin were administered to male and female rats. Mortality occurred at 9 mg/kg/day. The precoital period was generally prolonged at 9 mg/kg/day. No treatment related effects on fertility or mating performance were noted at doses  $\leq 1$  mg/kg/day.*

#### 4.4.4.2. Information From the Published Literature

In a study of CF-1 mice, male and female mice selected on the basis of P-glycoprotein genotype were mated and the pregnant dams exposed during gestation to the known P-glycoprotein substrate, L-652,280, the 8,9 Z photoisomer of the naturally occurring avermectin B<sub>1a</sub>, known to produce cleft palate in mice. Fetal examination demonstrated that within individual litters, fetuses deficient in P-glycoprotein (-/-) were 100% susceptible to cleft palate, whereas their +/- heterozygote littermates were less sensitive. The homozygous ++ fetuses with abundant P-glycoprotein were totally insensitive at the doses tested. The degree of chemical exposure of fetuses within each litter was inversely related to expression of placental P-glycoprotein, which was determined by the fetal genotype ([Lankas et al., 1998](#)).

#### 4.4.4.3. Information From the SBAs of Ivermectin Products

Teratology (segment II) studies have been conducted in mice, rats, and rabbits as part of the approval for Stromectol. These studies are summarized in [Table 6](#).

**Table 6 Reproductive Toxicology Studies Conducted With Oral Ivermectin**

| Species          | Dams per Group     | Daily Dose (mg/kg)             | NOAEL; HED                                                                           | Adverse Maternal Effects                                                                                                                                                     | Adverse Fetal Effects                                                                                                                                                                                      |
|------------------|--------------------|--------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mice (gd 6 – 15) | 20–25 <sup>a</sup> | 0, 0.1, 0.2, 0.4, 0.8, and 1.6 | <ul style="list-style-type: none"> <li>• 0.1 mg/kg;</li> <li>• 0.08 mg/kg</li> </ul> | <ul style="list-style-type: none"> <li>• Tremors and convulsions in some dams following 0.2 mg/kg/day</li> <li>• Some maternal deaths at 0.4 mg/kg/day and higher</li> </ul> | <ul style="list-style-type: none"> <li>• Teratogenic effects at 0.4 mg/kg/day and above</li> <li>• Cleft palate in 0.4, 0.8, and 1.6 mg/kg/day groups</li> <li>• Exencephaly in 0.8 mg/kg group</li> </ul> |
| Rats (gd 6 – 17) | 25                 | 0, 2.5, 5, and 10              | <ul style="list-style-type: none"> <li>• 2.5 mg/kg;</li> <li>• 0.4 mg/kg</li> </ul>  | <ul style="list-style-type: none"> <li>• At 2.5 mg/kg, some maternal deaths and some pre-implantation loss</li> </ul>                                                        | <ul style="list-style-type: none"> <li>• Incomplete bone ossification in 5 and 10 mg/kg/day groups</li> <li>• Cleft palate and “wavy ribs” in 10 mg/kg group</li> </ul>                                    |

**Table 6 Reproductive Toxicology Studies Conducted With Oral Ivermectin**

| Species             | Dams per Group | Daily Dose (mg/kg) | NOAEL; HED                                                                           | Adverse Maternal Effects                                                                                                                                           | Adverse Fetal Effects                                                                                         |
|---------------------|----------------|--------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Rabbits (gd 6 – 18) | 16             | 0, 1.5, 3, and 6   | <ul style="list-style-type: none"> <li>• 1.5 mg/kg;</li> <li>• 0.48 mg/kg</li> </ul> | <ul style="list-style-type: none"> <li>• At 1.5 mg/kg, decreased maternal body weights and some abortions</li> <li>• Increase in number of dead fetuses</li> </ul> | <ul style="list-style-type: none"> <li>• Cleft palate and clubbed forepaws in 3 and 6 mg/kg groups</li> </ul> |

<sup>a</sup>This entry is the accumulated results from several studies in mice.

gd = gestational day; HED = human equivalent dose; NOAEL = No Observed Adverse Effects Level

Source: Merck SBA ([FDA, 1996](#))

Since completion of these studies in CF-1 mice, it has been established that a subpopulation of CF-1 mice contain a spontaneous mutation in the P-glycoprotein *mdr1a* gene, leading to a loss of expression in the placenta, as well as brain and intestine ([Lankas et al., 1998](#)). As the original reproductive toxicology studies for the approval of Stromectol were conducted in CF-1 mice, the teratogenic effects of ivermectin in mice are likely to be, at least in part, accounted for by sensitivity to ivermectin in this strain.

Additional reproduction (segment III) studies that were conducted in rats show that ivermectin produces adverse events (AEs) in neonates (delayed development, increased pup mortality). These effects occurred at maternal doses of 1.6 mg/kg/day and above. It was also shown that the compound was secreted in the milk of lactating rats ([FDA, 1996](#)).

#### **4.4.5. Genotoxicity**

##### **4.4.5.1. Information From the Approved Labeling of Ivermectin Products**

The following genotoxicity information for ivermectin (*italicized*) is provided in the drug product labeling from Edenbridge Pharmaceuticals, LLC ([Edenbridge, 2014](#)) and is applicable to all approved ivermectin products:

*Ivermectin was not genotoxic in vitro in the Ames microbial mutagenicity assay of Salmonella typhimurium strains TA1535, TA1537, TA98, and TA100 with and without rat liver enzyme activation, the Mouse Lymphoma Cell Line L5178Y (cytotoxicity and mutagenicity) assays, or the unscheduled DNA synthesis assay in human fibroblasts.*

The following information for ivermectin (*italicized*) is provided in the Soolantra labeling ([Galderma Laboratories, 2018](#)) and is applicable to all approved ivermectin products

*Ivermectin revealed no evidence of genotoxic potential based on the results of two in vitro genotoxicity tests (the Ames test and the L5178Y/TK+/-mouse lymphoma assay) and one in vivo genotoxicity test (rat micronucleus assay).*

#### **4.4.5.2. Information From the Published Literature**

Male Sprague Dawley rats were given intraperitoneal ivermectin at doses between 0.2 mg/kg and 3.2 mg/kg body weight. Percentages of mitotic and aberrant bone marrow cells were assessed. The results indicated that ivermectin by itself, at doses higher than the recommended dose, induced significant levels of cytogenetic toxicity. The minimum detectable toxic dose of ivermectin was reported to be 0.4 mg/kg (HED = 0.06 mg/kg) ([Khalil and Abu Samrah, 2018](#)).

### **5. EFFECTS IN HUMANS**

#### **5.1. Clinical Pharmacology**

##### **5.1.1. Ivermectin Metabolism in Humans**

The following information for ivermectin metabolism (*italicized*) is provided in the drug product labeling from Edenbridge Pharmaceuticals, LLC ([Edenbridge, 2014](#)) and is applicable to all approved ivermectin products:

*In vitro studies using human liver microsomes and recombinant CYP450 enzymes have shown that ivermectin is primarily metabolized by CYP3A4. Depending on the in vitro method used, CYP2D6 and CYP2E1 were also shown to be involved in the metabolism of ivermectin but to a significantly lower extent compared to CYP3A4. The findings of in vitro studies using human liver microsomes suggest that clinically relevant concentrations of ivermectin do not significantly inhibit the metabolizing activities of CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2E1.*

Ivermectin is metabolized by CYP3A enzymes and transported across the blood-brain barriers by the drug transporter P-glycoprotein (P-gp, ABCB1). While no genetic variants with a clearly characterized functional impact on enzyme activity are known for the CYP3A isoform CYP3A4, the second isoform expressed in adults, CYP3A5, is well known for its genetic polymorphism. Of particular importance is the variant \*3 (rs776746) that affects mRNA splicing and results in mRNA degradation and thus no production of a functional protein. While a majority of individuals of European ancestry are homozygous carriers of the \*3 variant and thus have no CYP3A5 activity ("nonexpressers"), the functional allele, \*1, is more common in African populations, resulting in an increased frequency of CYP3A5 "expresser" phenotypes. In addition, 2 missense variants, \*6 and \*7, occur at a relevant frequency in African populations. Given this extensive polymorphism, interindividual differences in the CYP3A5 phenotype could affect the metabolism of ivermectin and potentially also the susceptibility to adverse effects or individual dose requirements. A small study in patients from Ghana suggested an impact of CYP3A5\*1/\*3 on response to ivermectin ([Kudzi et al., 2010](#)). However, the impact of CYP3A5 genetic variation on ivermectin pharmacokinetics and adverse drug reactions has not been assessed. Similarly, several genetic polymorphisms are known in the gene encoding P-gp, ABCB1. Given the neurological adverse effects observed with ivermectin and the important role of P-gp in drug transport across the blood-brain barrier, ABCB1 genetic variation may impact the susceptibility to ivermectin-induced neurological adverse effects. In a small study in Cameroon ([Bourguinat et al., 2010](#)), DNA sequencing was

conducted on 4 patients who experienced post-ivermectin serious adverse events (SAEs) and 9 non-SAE matched controls. The results showed that haplotypes associated with altered drug disposition were present as homozygotes in 2 of the SAE patients (50%), but absent as homozygotes in the controls (0%). These haplotypes were that was also associated with CNS adverse effects from codeine ([Sistonen et al., 2012](#)).

### 5.1.2. Ivermectin Pharmacokinetics in Humans

The AUC and  $C_{\max}$  for ivermectin appear to be linear through oral doses of 2000 mcg/kg. Although one study ([Guzzo et al., 2002](#)) noted that AUC and  $C_{\max}$  did not increase between 60 and 90 mg doses (1000 and 1500 mcg/kg, respectively), when all data are combined, linearity becomes apparent ([Table 7](#) and [Figure 2](#)).

**Table 7 Ivermectin AUC and  $C_{\max}$  from All Sources**

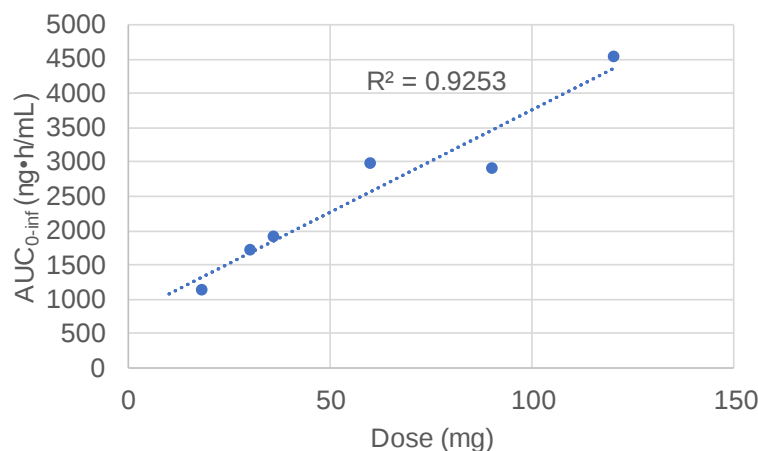
| Dose    |                           | $C_{\max}$ (ng/mL) | AUC <sub>0-inf</sub> (ng•h/mL) | Source                               |
|---------|---------------------------|--------------------|--------------------------------|--------------------------------------|
| Nominal | Weight-based <sup>a</sup> |                    |                                |                                      |
| 10      | 166.7 mcg/kg              | 46.6 ± 21.9        | NR                             | <a href="#">(Merck, 2009)</a>        |
| 10      | 166.7 mcg/kg              | 30.6 ± 15.6        | NR                             |                                      |
| 30      | 500 mcg/kg                | 84.8 ± 42.7        | 1724.3                         | <a href="#">(Guzzo et al., 2002)</a> |
| 60      | 1000 mcg/kg               | 165.2 ± 98.6       | 2984                           |                                      |
| 90      | 1500 mcg/kg               | 158.1 ± 87.6       | 2910.2                         |                                      |
| 120     | 2000 mcg/kg               | 247.8 ± 158.9      | 4547.7                         |                                      |
| 18      | 300 mcg/kg                | 64.1               | NR                             | <a href="#">(Smit et al., 2019)</a>  |
| 36      | 600 mcg/kg                | 105.2              | NR                             |                                      |
| 18      | 300 mcg/kg                | 45.23              | 1132.5                         | <a href="#">(Muñoz et al., 2018)</a> |
| 36      | 600 mcg/kg                | 78.04              | 1906.68                        |                                      |

<sup>a</sup> Based on a 60-kg adult

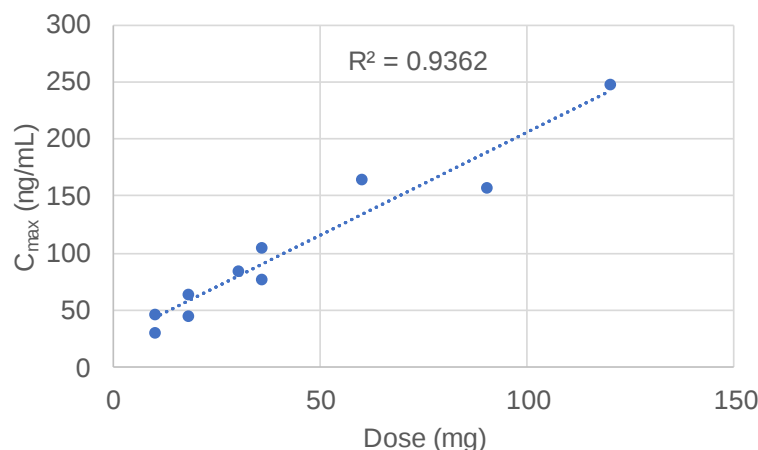
AUC<sub>0-inf</sub> = area under the concentration-time curve from time zero extrapolated to infinity;  $C_{\max}$  = maximum plasma concentration; NR = not reported

**Figure 2 Ivermectin AUC and C<sub>max</sub> Over the Dose Range 10–120 mg (167–2000 mcg/kg)**

**A. AUC<sub>0-inf</sub>**



**B. C<sub>max</sub>**



Source: Data in [Table 7](#)

The data above indicate a similar half-life for oral ivermectin (approximately 18 hours) for high-dose (30–120 mg, [Guzzo et al., 2002](#)) compared with the data in the Ivermectin Tablet product labeling ( [Edenbridge, 2014](#)). Importantly, the studies consistently demonstrate rapid clearance of ivermectin and little accumulation after daily dosing or 3-times per week dosing.

#### 5.1.2.1. Information From the Approved Labeling of Ivermectin Products

The following PK information for ivermectin (*italicized*) is provided in the drug product labeling from Edenbridge Pharmaceuticals, LLC ([Edenbridge, 2014](#)) and is applicable to all approved ivermectin products, although the exact PK values may differ slightly by product:

*Following oral administration of ivermectin, plasma concentrations are approximately proportional to the dose. In two studies, after single 12-mg doses*

*of Ivermectin Tablets in fasting healthy volunteers (representing a mean dose of 165 mcg/kg), the mean peak plasma concentrations of the major component ( $H_2B_{1a}$ ) were 46.6 ( $\pm 21.9$ ) (range: 16.4– 101.1) and 30.6 ( $\pm 15.6$ ) (range: 13.9–68.4) ng/mL, respectively, at approximately 4 hours after dosing. Ivermectin is metabolized in the liver, and ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 days, with less than 1% of the administered dose excreted in the urine. The plasma half-life of ivermectin in man is approximately 18 hours following oral administration.*

*The safety and pharmacokinetic properties of ivermectin were further assessed in a multiple-dose clinical pharmacokinetic study involving healthy volunteers. Subjects received oral doses of 30 to 120 mg (333 to 2000 mcg/kg) ivermectin in a fasted state or 30 mg (333 to 600 mcg/kg) ivermectin following a standard high-fat (48.6 g of fat) meal. Administration of 30 mg ivermectin following a high-fat meal resulted in an approximate 2.5-fold increase in bioavailability relative to administration of 30 mg ivermectin in the fasted state.*

#### **5.1.2.2. Information From the Published Literature**

Several studies in the literature investigated the PK characteristics of high doses of oral ivermectin. These studies are summarized below.

##### **Guzzo 2002**

Safety and PK of ivermectin (oral) administered in higher and/or more frequent doses than currently approved for human use were evaluated in a double-blind, placebo-controlled, dose escalation study (Guzzo et al., 2002). Pharmacokinetic data are discussed below. Subjects (n = 68) were assigned to 1 of 4 panels (3:1, ivermectin/placebo):

- 30 mg x 3 times per week. This group also received a single dose with food after a 1-week washout. This dose is equivalent to 500  $\mu$ g/kg in a 60-kg adult
- 60 mg x 3 times per week. This dose is equivalent to 1000  $\mu$ g/kg in a 60-kg adult
- 90 mg, single dose. This dose is equivalent to 1500  $\mu$ g/kg in a 60-kg adult
- 120 mg, single dose. This dose is equivalent to 2000  $\mu$ g/kg in a 60-kg adult

Following single doses of 30 to 120 mg, area under the concentration-versus-time curve (AUC) and time to ( $T_{max}$ ) maximum plasma concentration ( $C_{max}$ ) were generally dose proportional, with time to maximum plasma concentration ( $t_{max}$ ) ~4 hours and half-life ( $t_{1/2}$ ) ~18 hours (Table 8). The geometric mean AUC of 30 mg ivermectin was 2.6 times higher when administered with food.

**Table 8 Pharmacokinetic Parameters of High-dose Ivermectin by Treatment Regimen**

| Parameter                                           | Fed                | Fasted            |                    |                    |                    |                    |                    |
|-----------------------------------------------------|--------------------|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
|                                                     | 30 mg<br>(n = 11)  | 30 mg<br>(n = 12) | 30 mg<br>(n = 12)  | 60 mg<br>(n = 12)  | 60 mg<br>(n = 12)  | 90 mg<br>(n = 12)  | 120 mg<br>(n = 12) |
|                                                     | Day 1              | Day 1             | Day 7              | Day 1              | Day 7              | Day 1              | Day 1              |
| <b>AUC<sub>0-∞</sub><br/>(ng•h/ml)<sup>a</sup></b>  | 4564.6 ±<br>1892.5 | 1724.3 ±<br>830.5 | 2819.4 ±<br>1691.2 | 2984.0 ±<br>1530.1 | 6061.7 ±<br>4243.7 | 2910.2 ±<br>1801.9 | 4547.7 ±<br>2402.9 |
| <b>AUC<sub>0-60</sub><br/>(ng•h/ml)<sup>b</sup></b> | NA                 | 1166.3            | 1444.3             | 2099.3             | 2947.2             | NA                 | NA                 |
| <b>AUC<sub>0-∞</sub><br/>(ng•h/ml)<sup>b</sup></b>  | 3951.9             | 1538.4            | NA                 | NA                 | NA                 | NA                 | NA                 |
| <b>C<sub>max</sub><br/>(ng/ml)<sup>a</sup></b>      | 260.5 ±<br>172.1   | 84.8 ±<br>42.7    | 87.0 ±<br>43.2     | 165.2 ±<br>98.6    | 186.2 ±<br>130.8   | 158.1 ±<br>87.6    | 247.8 ±<br>158.9   |
| <b>t<sub>1/2</sub> (h)<sup>c</sup></b>              | 15.0               | 20.1              | 17.7               | 19.6               | 17.5               | 18.8               | 19.1               |
| <b>t<sub>max</sub> (h)<sup>a</sup></b>              | 4.6 ± 0.9          | 4.3 ± 1.0         | 4.2 ± 0.9          | 3.6 ± 0.9          | 4.0 ± 1.1          | 4.9 ± 1.8          | 4.2 ± 0.9          |

Data are provided as mean ± standard deviation.

In a 60-kg adult, the 30-mg dose is the equivalent to 500 µg/kg, and the 60-mg dose is equivalent to 1000 µg/kg

<sup>a</sup> Arithmetic mean

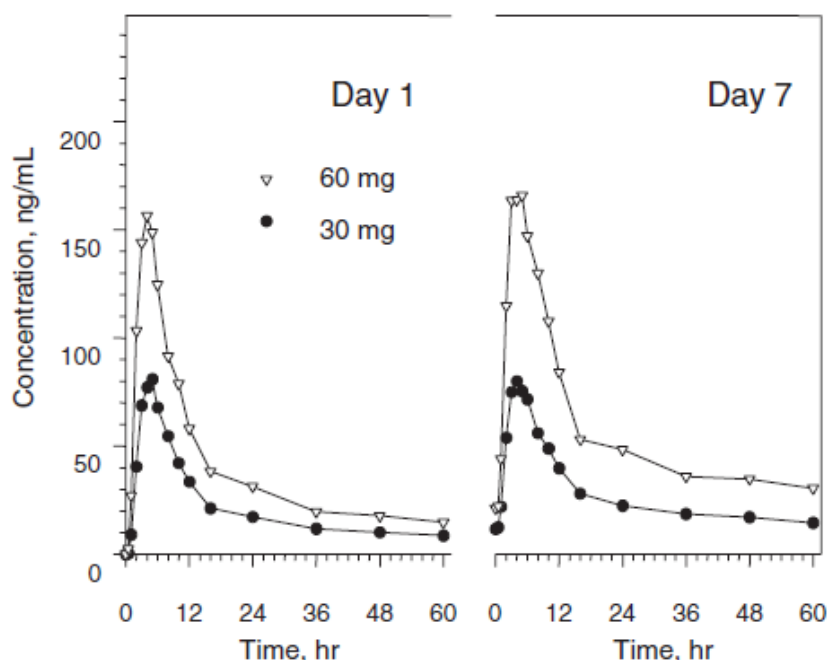
<sup>b</sup> Geometric mean

<sup>c</sup> Harmonic mean

Source: [Guzzo et al., 2002](#)

Geometric mean AUC ratios (Day 7/Day 1) were 1.24 and 1.40 for the 30- and 60-mg doses, respectively ([Figure 3](#)), indicating that the accumulation of ivermectin given every fourth day is minimal, consistent with a short t<sub>1/2</sub> relative to the dosing interval (72 hours) ([Guzzo et al., 2002](#)).

**Figure 3 Mean Plasma Concentration Profiles of Ivermectin Following Multiple Oral Doses of 30 and 60 mg Given Fasted on Days 1, 4, and 7**



Source: [Guzzo et al., 2002](#), Figure 2

## Smit 2019

Smit et al (2019) assessed the relationship between ivermectin blood concentrations and the observed mosquitocidal effects against *Anopheles gambiae* ssp. The study evaluated 141 adults with uncomplicated malaria in Kenya who were randomly assigned to receive 3 days of ivermectin at doses of 0, 300, or 600 µg/kg/day, plus daily dihydroartemisinin-piperaquine (DP).

During 28 days of follow-up, 1,393 venous and 335 paired capillary plasma samples were collected. Pharmacokinetic parameters were evaluated and are shown in [Table 9](#).

**Table 9 Comparison of Ivermectin Pharmacokinetic Parameters From Plasma Versus Simultaneous PK: PD Modeling**

| Parameter                         | Ivermectin Dose (µg/kg/day) | PK Parameters (Sequential PK: PD Model) | PK parameters (Simultaneous PK: PD Model) |
|-----------------------------------|-----------------------------|-----------------------------------------|-------------------------------------------|
| $C_{max}$ (ng/mL)                 | 300                         | 64.1 (29.7–129.9)                       | 69.4 (34.1–196.3)                         |
|                                   | 600                         | 105.2 (44.5–482.5)                      | 118.9 (45.2–455.1)                        |
| $T_{max}$ (hours) after last dose | 300                         | 5.0 (1.4–8.8)                           | 3.9 (0.75–7.6)                            |
|                                   | 600                         | 3.5 (0.40–7.5)                          | 2.3 (0.43–8.2)                            |
| $t_{1/2}$ (hours)                 | 300                         | 5.1 (2.2–12.6)                          | 2.9 (1.1–7.8)                             |
|                                   | 600                         | 4.7 (1.7–12.5)                          | 3.2 (0.90–8.5)                            |

**Table 9 Comparison of Ivermectin Pharmacokinetic Parameters From Plasma Versus Simultaneous PK: PD Modeling**

| Parameter                              | Ivermectin Dose (µg/kg/day) | PK Parameters (Sequential PK: PD Model) | PK parameters (Simultaneous PK: PD Model) |
|----------------------------------------|-----------------------------|-----------------------------------------|-------------------------------------------|
| AUC <sub>0-28</sub> days (hours/µg/mL) | 300                         | 5.5 (2.5–8.3)                           | 5.0 (1.6–8.3)                             |
|                                        | 600                         | 10.0 (1.7–22.3)                         | 9.3 (2.1–25.0)                            |

Data are provided as median ± interindividual variability (%)

Source: [Smit et al., 2019](#)

Ivermectin PK parameters were best described by a two-compartment oral absorption model. The initial sequential model, utilizing only plasma concentration data to fit the PK data, resulted in the parameters described in [Table 9](#). In addition, clearance was reported to be 10.9 L/hour. One limitation of this study is that, in the ivermectin arms post-treatment, concentrations were below the limit of quantification for 277 of 805 (34.4%) venous and 44 of 224 (19.6%) capillary samples, predominantly at later time points due to a relatively high lower limit of quantification (LLOQ) (venous: 5 ng/mL, capillary: 10 ng/mL) compared to that used in other studies ( $\leq 2.5$  ng/mL).

#### Munoz 2018

Munoz et al ([2018](#)) conducted a Phase I clinical trial with 54 healthy adult volunteers who sequentially received 2 experimental treatments using a new 18 mg ivermectin tablet in a fixed-dose strategy of 18 mg (300 µg/kg in a 60-kg adult) and 36 mg (600 µg/kg in a 60-kg adult) single-dose regimens, compared to the standard, weight-based 200 µg/kg, regimen. The PK parameters of oral ivermectin are shown in [Table 10](#).

**Table 10 PK Parameters of Ivermectin for the Entire Study Population; Arithmetic Mean (Standard Deviation)**

| Parameters                    | Weight Adjusted Reference Treatment | 18 mg Fixed-dose  | 36 mg Fixed-dose  |
|-------------------------------|-------------------------------------|-------------------|-------------------|
| AUC <sub>0-t</sub> (ng·h/mL)  | 860.13 (384.13)                     | 885.92 (514.23)   | 1500.40 (838.40)  |
| AUC <sub>0-∞</sub> (ng·h/mL)  | 1087.81 (505.16)                    | 1132.50 (684.05)  | 1906.68 (1136.50) |
| C <sub>max</sub> (ng/mL)      | 43.19 (18.11)                       | 45.23 (24.29)     | 78.04 (43.11)     |
| t <sub>max</sub> <sup>a</sup> | 4.15 (1.20)                         | 4.33 (1.94)       | 4.11 (1.07)       |
| t <sub>1/2</sub> (h)          | 80.66 (33.33)                       | 80.98 (48.51)     | 90.56 (58.17)     |
| V/F (L)                       | 1822.29 (857.21)                    | 2266.20 (1215.22) | 3000.97 (1677.28) |
| Cl/F (L/h)                    | 17.31 (9.16)                        | 24.40 (19.14)     | 27.33 (17.71)     |

<sup>a</sup> Units for T<sub>max</sub> were not provided in the article but are likely to be hours

Source: [Muñoz et al., 2018](#)

### 5.1.3. Population Subgroups

The following information for ivermectin (*italicized*) is provided in the drug product labeling from Edenbridge Pharmaceuticals, LLC ([Edenbridge, 2014](#)) and is applicable to all approved ivermectin products:

#### ***Nursing Mothers***

*Ivermectin is excreted in human milk in low concentrations. Treatment of mothers who intend to breastfeed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the newborn.*

#### ***Pediatric Use***

*Safety and effectiveness in pediatric patients weighing less than 15 kg have not been established.*

#### ***Geriatric Use***

*Clinical studies of ivermectin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, treatment of an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.*

## 5.2. Efficacy and Safety

### 5.2.1. Summary of Clinical Efficacy – COVID-19

See [Section 1.3.1](#) above.

### 5.2.2. Summary of Clinical Safety

The approved ivermectin doses are as follows:

- United States:
  - Strongyloidiasis: single dose of 200 µg/kg
  - Onchocerciasis: single dose of 150 µg/kg, repeated every 3–12 months as needed
- Australia
  - Strongyloidiasis: single dose of 200 µg/kg, repeated every 6–12 months as needed
  - Onchocerciasis: single dose of 150 µg/kg, repeated every 6–12 months as needed
  - Scabies: 2 doses of 200 µg/kg given approximately 1–2 weeks apart (more than 3 doses may be given for moderate to severe cases)
- France and the Netherlands
  - Strongyloidiasis: single dose of 200 µg/kg

- Scabies: single dose of 200 µg/kg, second dose may be given within 2 weeks
- Microfilaremia:
  - Single dose of 150–200 µg/kg, repeated every 6–12 months
  - Single dose of 300–400 µg/kg if given only every 12 months

There are multiple studies in the literature that contain safety data on subjects receiving higher doses of ivermectin. The extent of exposure includes 11,893 subjects receiving at least one dose of 300 µg/kg (Table 12), 11,839 subjects receiving 400 µg/kg (Table 133), and 541 patients receiving 600 µg/kg (Table 144). Twelve patients each were exposed to single doses of 1500 µg/kg and 2000 µg/kg. Pediatric ( $\geq 15$  kg) exposure to high-dose ivermectin includes 2 studies in which 398 patients received a 400 µg/kg dose and 52 subjects received a 200–400 µg/kg dose (Table 111).

Ivermectin has a favorable safety profile. From 1998 to 2018, 3.6 billion treatments have been approved by various regulatory authorities, including WHO, for distribution as part of mass drug administration for onchocerciasis and lymphatic filariasis control (Mectizan Donation Program, 2018). In the published literature, an oral dose of 400 µg/kg repeated after 1 week was found to be safe in children with head lice (Chosidow et al., 2010). Oral doses of 800 µg/kg of ivermectin repeated yearly or every 3 months were safely tested in 339 adults with onchocerciasis (Awadzi et al., 1995; Awadzi et al., 1999; Kamgno et al., 2004).

The safety findings for these studies indicate that high-dose oral ivermectin is generally well-tolerated. Most adverse events were transient and not serious. Some events, such as pruritus and edema, were likely the result of inflammatory reactions occurring in the skin due to killing of dermal nematodes. The occurrence of these events was dose-dependent and diminished with subsequent treatment with ivermectin, presumably due to clearance of the nematode parasites (Kamgno et al., 2004).

#### 5.2.2.1. Safety Data From the Approved Labeling of Ivermectin Products

The following safety information for ivermectin (*italicized*) is provided in the drug product labeling from Edenbridge Pharmaceuticals, LLC (Edenbridge, 2014) and is applicable to all approved ivermectin products:

##### **WARNINGS**

*Historical data have shown that microfilaricidal drugs, such as diethylcarbamazine citrate (DEC-C), might cause cutaneous and/or systemic reactions of varying severity (the Mazzotti reaction) and ophthalmological reactions in patients with onchocerciasis. These reactions are probably due to allergic and inflammatory responses to the death of microfilariae. Patients treated with [ivermectin] for onchocerciasis may experience these reactions in addition to clinical adverse reactions possibly, probably, or definitely related to the drug itself.*

*The treatment of severe Mazzotti reactions has not been subjected to controlled clinical trials. Oral hydration, recumbency, intravenous normal saline, and/or parenteral corticosteroids have been used to treat postural hypotension. Antihistamines and/or aspirin have been used for most mild to moderate cases.*

## **PRECAUTIONS**

### **General**

*Rarely, patients with onchocerciasis who are also heavily infected with Loa loa may develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide. In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival hemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma. This syndrome has been seen very rarely following the use of ivermectin. In individuals who warrant treatment with ivermectin for any reason and have had significant exposure to Loa loa-endemic areas of West or Central Africa, pretreatment assessment for loiasis and careful post-treatment follow-up should be implemented.*

### **5.2.2.2. Safety Data From the Published Literature**

There are a large number of studies in the literature that support the safety of high doses of ivermectin. Most of these studies used the product manufactured by Merck Sharp & Dohme in Europe, which is the same as the United States product, Stromectol. A summary of AEs from the studies in the published literature using doses of 300 µg/kg or more is provided in [Table 111](#). Tabulations of the extent of exposure for each of the 3 doses levels are provided in [Table 122](#), [Table 133](#), and [Table 144](#). The studies demonstrate that administration of high doses of oral ivermectin is generally well tolerated in adults and children with head lice, infections caused by *Wuchereria bancrofti*, *Onchocerca volvulus*, *Plasmodium falciparum* malaria, or *Mansonella perstans*, and in healthy volunteers. Adverse events were transient and not serious.

In a pilot, randomized, controlled, open-label, multicenter trial, investigators examined the antiviral activity of ivermectin in COVID-19 patients. The study compared standard of care with and without ivermectin at 600 µg/kg/day for 5 days ([Krolewiecki et al., 2020](#)). While there was no difference in viral load reduction between groups, there was a significant difference in reduction of viral load in patients with higher median plasma ivermectin levels, and there was a positive correlation between ivermectin plasma concentration levels and viral decay rate ([Krolewiecki et al., 2020](#)).

**Table 11 Safety of Oral Ivermectin Administered at Doses of 300 µg/kg and Above**

| Source                             | Ivermectin Source                                                                                                                               | Number Exposed (Dose)                                                                                                             | Study Population                   | Adverse Events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Healthy Volunteers</b>          |                                                                                                                                                 |                                                                                                                                   |                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <a href="#">Guzzo et al., 2002</a> | Merck Sharp & Dohme (France)                                                                                                                    | <ul style="list-style-type: none"> <li>• 15 (30 mg)</li> <li>• 12 (60 mg)</li> <li>• 12 (90 mg)</li> <li>• 12 (120 mg)</li> </ul> | Healthy male and female volunteers | <p>No difference with controls.</p> <p>30 mg</p> <ul style="list-style-type: none"> <li>• Body as a whole 2/15 (13%)</li> <li>• Digestive system 1/15 (7%)</li> <li>• Musculoskeletal 2/15 (13%)</li> <li>• Nervous system 1/15 (7%)</li> <li>• Urogenital 1/15 (7%)</li> </ul> <p>60 mg</p> <ul style="list-style-type: none"> <li>• Body as a whole 1/12 (8%)</li> <li>• Digestive system 1/12 (8%)</li> <li>• Nervous system 4/12 (33%)</li> <li>• Skin 1/12 (8%)</li> </ul> <p>90 mg</p> <ul style="list-style-type: none"> <li>• Digestive system 1/12 (8%)</li> <li>• Nervous system 1/12 (8%)</li> </ul> <p>120 mg</p> <ul style="list-style-type: none"> <li>• None</li> </ul> |
| <a href="#">Muñoz et al., 2018</a> | <ul style="list-style-type: none"> <li>• 18 mg: Liconsa Laboratories (Spain)</li> <li>• 6 mg: Abbott Laboratories (Brazil) Revectina</li> </ul> | <ul style="list-style-type: none"> <li>• 57 (18 mg then 36 mg then 12–24 mg)</li> </ul>                                           | Healthy male and female volunteers | <ul style="list-style-type: none"> <li>• Headache (3/57 at 36 mg, 2/55 at 18 mg, 5/54 at 12–24 mg)</li> <li>• Dysmenorrhea (1/57 at 36 mg, 3/55 at 18 mg, 1/54 at 12–24 mg)</li> <li>• Throat pain (2/57 at 36 mg, 1/55 at 18 mg)</li> <li>• Cold (2/57 at 36 mg, 1/55 at 18 mg)</li> <li>• Diarrhea (1/57 at 36 mg, 2/54 at 12–24 mg)</li> <li>• Back pain (1/57 at 36 mg, 1/54 at 12–24 mg)</li> <li>• N = 1 for vaginal candidiasis, gastroenteritis, nausea, tooth pain, abdominal pain and prolonged coagulation time</li> </ul>                                                                                                                                                  |

**Table 11 Safety of Oral Ivermectin Administered at Doses of 300 µg/kg and Above**

| Source                                                     | Ivermectin Source            | Number Exposed (Dose)                                                                                                        | Study Population                                                    | Adverse Events                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------------------------------------------------|------------------------------|------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Patients with <i>Wuchereria bancrofti</i> infection</b> |                              |                                                                                                                              |                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <a href="#">Addiss et al., 1991</a>                        | Merck Sharp & Dohme (France) | <ul style="list-style-type: none"> <li>• 10 (20 µg/kg then 400 µg/kg on day 5)</li> </ul>                                    | Males and females with <i>Wuchereria bancrofti</i> infection        | Treatments were well tolerated. Clinical signs and symptom severity were lower following high doses than clearing doses.                                                                                                                                                                                                                                                                                                                                         |
| <a href="#">Addiss et al., 1993</a>                        | Merck Sharp & Dohme (UK)     | Days 1 and 5<br><ul style="list-style-type: none"> <li>• 9 (20 µg/kg then 400 µg/kg)</li> </ul>                              | Males and females with <i>Wuchereria bancrofti</i> infection        | Severity of AEs did not increase with dose. Most common AEs: headache, myalgias, weakness, lethargy & fever (study arms of AEs not specified)                                                                                                                                                                                                                                                                                                                    |
| <a href="#">Addiss et al., 1997</a>                        | Merck Sharp & Dohme (UK)     | <ul style="list-style-type: none"> <li>• 28 (200–400 µg/kg)</li> <li>• 24 (200–400 µg/kg with 400 mg albendazole)</li> </ul> | Male and female children with <i>Wuchereria bancrofti</i> infection | Treatment was well tolerated. Adverse reactions were common with placebo. <ul style="list-style-type: none"> <li>• Fever 60/83 (69%)</li> <li>• Headache 62/83 (75%)</li> <li>• Myalgia 31/83 (37%)</li> <li>• Cough 35/83 (42%)</li> </ul>                                                                                                                                                                                                                      |
| <a href="#">Bockarie et al., 1998</a>                      | Not specified                | <ul style="list-style-type: none"> <li>• 1077 (400 µg/kg with 6 mg/kg DEC)</li> </ul>                                        | Males and females with <i>Wuchereria bancrofti</i> infection        | No side effects requiring medical intervention other than antipyretics                                                                                                                                                                                                                                                                                                                                                                                           |
| <a href="#">Cartel et al., 1992</a>                        | Merck Sharp & Dohme (France) | <ul style="list-style-type: none"> <li>• 37 (400 µg/kg)</li> </ul>                                                           | Males and female carriers of <i>Wuchereria bancrofti</i>            | <ul style="list-style-type: none"> <li>• Headache 11/7 (55/41%)</li> <li>• Myalgia 11/6 (55/35%)</li> <li>• Arthralgia 9/8 (45/47%)</li> <li>• Chills 9/0 (45/0%)</li> <li>• Fever 8/7 (40/41%)</li> <li>• Anorexia 4/0 (20/0%)</li> <li>• Weakness 3/0 (15/0%)</li> <li>• Cough 2/0 (10/0%)</li> <li>• Vertigo 1/1 (5/6%)</li> <li>• Nausea 1/1 (5/6%)</li> <li>• Vomiting 1/0 (5/0%)</li> <li>• Dyspnea 1/0 (5/0%)</li> <li>• Gastralgia 0/1 (0/6%)</li> </ul> |

**Table 11 Safety of Oral Ivermectin Administered at Doses of 300 µg/kg and Above**

| Source                               | Ivermectin Source                       | Number Exposed (Dose)                                                                                                                                        | Study Population                                             | Adverse Events                                                                                                                                                                                                                                                                                                                                 |
|--------------------------------------|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                      |                                         |                                                                                                                                                              |                                                              | <ul style="list-style-type: none"> <li>• Malaise 0/11 (0/65%)</li> </ul>                                                                                                                                                                                                                                                                       |
| <a href="#">Dembele et al., 2010</a> | Merck – Mectizan Donation Program (USA) | <ul style="list-style-type: none"> <li>• 18 (150 µg/kg with 400 mg albendazole) annual</li> <li>• 19 (400 µg/kg with 800 mg albendazole) 2 x year</li> </ul> | Males and females with <i>Wuchereria bancrofti</i> infection | Annual <ul style="list-style-type: none"> <li>• Urticaria (n = 1)</li> <li>• Angioedema (n = 2)</li> </ul> 2 x Year <ul style="list-style-type: none"> <li>• Epigastric pain (n = 1)</li> <li>• Angioedema (n = 1)</li> <li>• Abdominal pain (n = 1)</li> <li>• Diarrhea (n = 1)</li> </ul>                                                    |
| <a href="#">Dreyer et al., 1995a</a> | Not specified                           | <ul style="list-style-type: none"> <li>• 11 (20 µg/kg then 400 µg/kg day 4)</li> </ul>                                                                       | Males with <i>Wuchereria bancrofti</i> infection             | In patients receiving ivermectin only: <ul style="list-style-type: none"> <li>• Fever 15/33 (46%)</li> <li>• Malaise 9/33 (27%)</li> <li>• GI 6/33 (18%)</li> <li>• Respiratory 11/33 (33%)</li> <li>• Neurological 5/33 (15%)</li> <li>• Local pain 3/33 (9%)</li> <li>• Local inflammation 3/33 (9%)</li> <li>• Renal 11/33 (33%)</li> </ul> |
| <a href="#">Dreyer et al., 1995b</a> | Not specified                           | <ul style="list-style-type: none"> <li>• 15 (400 µg/kg)</li> </ul>                                                                                           | Males with <i>Wuchereria bancrofti</i> infection             | <ul style="list-style-type: none"> <li>• 10/15 (67%) patients had AEs.</li> <li>• The most common were fever, headache, myalgia and hematuria.</li> <li>• Severity was related to pretreatment microfilarial density (data not shown)</li> </ul>                                                                                               |
| <a href="#">Ismail et al., 2001</a>  | Merck Sharp & Dohme (France)            | <ul style="list-style-type: none"> <li>• 15 (400 µg/kg with 600 mg albendazole)</li> </ul>                                                                   | Males with <i>Wuchereria bancrofti</i> infection             | Treatments were well tolerated. Fever, headache, myalgia and weakness reported (study arms of AEs not specified)                                                                                                                                                                                                                               |
| <a href="#">Ismail et al., 1998</a>  | Merck Sharp & Dohme (France)            | <ul style="list-style-type: none"> <li>• 13 (400 µg/kg with 600 mg albendazole)</li> </ul>                                                                   | Males with <i>Wuchereria bancrofti</i> infection             | Treatments were well tolerated. Fever, headache, myalgia and weakness reported (study arms of AEs not specified)                                                                                                                                                                                                                               |

**Table 11 Safety of Oral Ivermectin Administered at Doses of 300 µg/kg and Above**

| Source                                                    | Ivermectin Source            | Number Exposed (Dose)                                                                                                                                                                 | Study Population                                             | Adverse Events                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------------------------------|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                           |                              | <ul style="list-style-type: none"> <li>• 12 (400 µg/kg with 6 mg/kg DEC)</li> </ul>                                                                                                   |                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <a href="#">Kazura et al., 1993</a>                       | Merck Sharp & Dohme (UK)     | <ul style="list-style-type: none"> <li>• 10 (220 µg/kg – single dose)</li> <li>• 10 (20 µg/kg then 400 µg/kg 4 days later)</li> </ul>                                                 | Males with <i>Wuchereria bancrofti</i> infection             | Fever <ul style="list-style-type: none"> <li>• 3/10 (220 µg/kg – single dose)</li> <li>• 1/10 (20 + 400 µg/kg)</li> </ul>                                                                                                                                                                                                                                                                                                       |
| <a href="#">Moulia-Pelat et al., 1996</a>                 | Merck Sharp & Dohme (France) | <ul style="list-style-type: none"> <li>• 19 (400 µg/kg) x 3 annual doses</li> <li>• 19 (400 µg/kg with 6 mg/kg DEC) x 3 annual doses</li> </ul>                                       | Males with <i>Wuchereria bancrofti</i> infection             | <ul style="list-style-type: none"> <li>• First dose: 34 patients had an AE (22 had level 1 and 12 had level 2).</li> <li>• Second dose (12 mo): 10 patients had an AE (7 had level 1 and 3 had level 2)</li> <li>• Third dose (24 mo): 4 patients had an AE (all level 1).</li> <li>• None of the AEs were serious, all recovered within 48 hours. AEs were highly correlated with the initial microfilaremia level.</li> </ul> |
| <a href="#">Nguyen et al., 1996</a>                       | Merck Sharp & Dohme (France) | <ul style="list-style-type: none"> <li>• 872 (100 µg/kg given 3 times then 400 µg/kg 3 times) 2 x year</li> </ul>                                                                     | Males and females with <i>Wuchereria bancrofti</i> infection | <ul style="list-style-type: none"> <li>• 1/865 (0.1%) with grade 1 AE</li> <li>• 29/865 (3.4%) with other AEs</li> </ul> Weakness, headache, myalgia, arthralgia, fever, anorexia, cough, shivering, dizziness, diarrhea, arrhythmia & hemoptysis                                                                                                                                                                               |
| <b>Patients with <i>Onchocerca volvulus</i> infection</b> |                              |                                                                                                                                                                                       |                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <a href="#">Awadzi et al., 1995</a>                       | Merck Sharp & Dohme (France) | <ul style="list-style-type: none"> <li>• 24 (600 µg/kg)</li> <li>• 17 (800 µg/kg)</li> </ul>                                                                                          | Males and females with <i>Onchocerca volvulus</i> infections | Mild reactions (non-dose dependent) <ul style="list-style-type: none"> <li>• Pain, fever, headache, rash, blood pressure &amp; pulse rate</li> </ul> (given as “reaction scores”)                                                                                                                                                                                                                                               |
| <a href="#">Awadzi et al., 1999</a>                       | Merck Sharp & Dohme (France) | <ul style="list-style-type: none"> <li>• 25 (400-550 µg/kg day 4)</li> <li>• 23 (600-750 µg/kg day 4)</li> <li>• 24 (800-950 µg/kg day 4)</li> <li>• 12 (1600 µg/kg day 4)</li> </ul> | Males with <i>Onchocerca volvulus</i> infections             | 800–1600 µg/kg were as safe as the 150 µg/kg dose                                                                                                                                                                                                                                                                                                                                                                               |

**Table 11 Safety of Oral Ivermectin Administered at Doses of 300 µg/kg and Above**

| Source                                     | Ivermectin Source            | Number Exposed (Dose)                                                                                                                                            | Study Population                                         | Adverse Events                                                                                                                                                                                                                                                                                                                                                                                                                         |
|--------------------------------------------|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <a href="#">Cooper et al., 1999</a>        | Not specified                | <ul style="list-style-type: none"> <li>• 8 (400 µg/kg)</li> <li>• 8 (600 µg/kg)</li> </ul>                                                                       | Males with heavy <i>Onchocerca volvulus</i> infections   | Dose-dependent increase in non-severe reactions <ul style="list-style-type: none"> <li>• fever, rash, blood pressure &amp; pulse rate (given as “reaction scores”)</li> </ul>                                                                                                                                                                                                                                                          |
| <a href="#">Kamgno et al., 2004</a>        | Merck Sharp & Dohme (France) | <ul style="list-style-type: none"> <li>• Males (n = 643)</li> <li>• 475 doses (400 µg/kg) administered</li> <li>• 1728 doses (800 µg/kg) administered</li> </ul> | Males with <i>Onchocerca volvulus</i> infections         | No severe AEs recorded.<br>AEs most common with less frequent dosing <ul style="list-style-type: none"> <li>• Edema, itching, backache</li> </ul> AEs more frequent with higher dosing <ul style="list-style-type: none"> <li>• Edematous swellings, subjective ocular troubles</li> </ul>                                                                                                                                             |
| <b>Other</b>                               |                              |                                                                                                                                                                  |                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <a href="#">Chosidow et al., 2010</a>      | Merck Sharp & Dohme (France) | <ul style="list-style-type: none"> <li>• 398 (400 µg/kg) days 1 and 8</li> </ul>                                                                                 | Male and female children with head lice                  | <ul style="list-style-type: none"> <li>• Seizure 1/398 (0.3%)</li> <li>• Impetigo 2/398 (0.5%)</li> <li>• Nausea/vomiting 1/398 (0.3%)</li> <li>• Gastroenteritis 3/398 (0.8%)</li> <li>• Convulsions 1/398 (0.3%)</li> <li>• Other events 30/398 (7.5%) <ul style="list-style-type: none"> <li>◦ GI, application site (pain/rash), fever, nasopharyngeal, headache, cough, pharyngolaryngeal &amp; psychomotor</li> </ul> </li> </ul> |
| <a href="#">Heukelbach et al., 2004</a>    | Solvay Farma S.A. (Brazil)   | <ul style="list-style-type: none"> <li>• 27 (300 µg/kg days 1 and 2)</li> </ul>                                                                                  | Males and females with stage II or III tungiasis lesions | AEs reported were not significantly different than placebo <ul style="list-style-type: none"> <li>• Headache 3/27 (11%)</li> <li>• Abdominal pain 2/27 (7%)</li> <li>• Sore throat 1/27 (4%)</li> </ul>                                                                                                                                                                                                                                |
| <a href="#">Martin-Prevel et al., 1993</a> | Merck Sharp & Dohme (France) | <ul style="list-style-type: none"> <li>• 16 (300 µg/kg)</li> <li>• 15 (400 µg/kg)</li> </ul>                                                                     | Males and females with <i>Loa loa</i> infection          | Treatment was well tolerated. <ul style="list-style-type: none"> <li>• Pruritus (60%)</li> <li>• Headache (16%)</li> <li>• Fever (8%)</li> <li>• Lumber myalgia (6.5%)</li> </ul>                                                                                                                                                                                                                                                      |

**Table 11 Safety of Oral Ivermectin Administered at Doses of 300 µg/kg and Above**

| Source                                     | Ivermectin Source             | Number Exposed (Dose)                                                                        | Study Population                                                        | Adverse Events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------------------|-------------------------------|----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                            |                               |                                                                                              |                                                                         | <ul style="list-style-type: none"> <li>• Diarrhea (6.5%)</li> <li>• Abdominal pain (1.5%)</li> <li>• Dizziness (1.5%)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                    |
| <a href="#">Smit et al., 2018</a>          | Elea Laboratories (Argentina) | <ul style="list-style-type: none"> <li>• 48 (300 µg/kg)</li> <li>• 47 (600 µg/kg)</li> </ul> | Males and females with symptomatic <i>Plasmodium falciparum</i> malaria | 300 µg/kg disorders <ul style="list-style-type: none"> <li>• Eye 2/48 (4%)</li> <li>• General 2/48 (4%)</li> <li>• Musculoskeletal 1/48 (2%)</li> <li>• Nervous system 2/48 (4%)</li> <li>• Abnormal ECG 1/48 (2%)</li> </ul> 600 µg/kg disorders <ul style="list-style-type: none"> <li>• Eye 4/45 (9%)</li> <li>• General 1/45 (2%)</li> <li>• Immune system 1/45 (2%)</li> <li>• Nervous system 2/45 (4%)</li> <li>• Vascular 1/45 (2%)</li> <li>• Pneumonia 4/45 (9%)</li> <li>• Bee sting 1/45 (2%)</li> </ul> |
| <a href="#">van den Enden et al., 1993</a> | Not specified                 | <ul style="list-style-type: none"> <li>• 7 (600 µg/kg)</li> </ul>                            | Males and females with <i>Mansonella perstans</i> infection             | One patient reported a mild pruritic reaction                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

AE = adverse event; DEC = diethylcarbamazine; ECG = electrocardiogram; GI = gastrointestinal; UK = United Kingdom; USA = United States of America

## Pediatric Exposure

Of note, two of the studies in [Table 11](#) assessed the safety of ivermectin in children at doses higher than the approved dose. In the first study, oral ivermectin at a dose of 400 µg/kg or topical malathion lotion was administered to children with live lice not eradicated by prior treatment with topical insecticide ([Chosidow et al., 2010](#)). The study population was predominantly female (86.9%), with a median age of 10 years (interquartile range, 7 to 14) and a mean weight of 40 ± 22 kg. There were no significant differences in the frequency of adverse events between the two treatment groups.

Two serious clinical adverse events were reported. A total of 7 of 398 patients (1.8%) in the ivermectin group and 5 of 414 patients (1.2%) in the malathion group discontinued treatment because of an adverse event; only 3 events were judged to be severe. The frequencies of adverse events were generally similar among the age groups of 2 to 5 years, 6 to 12 years, and older than 12 years, but in absolute terms, the youngest group had the fewest events.

In a second study ([Addiss et al., 1997](#)), children 5–11 years of age infected with *Wuchereria bancrofti* were randomly assigned to 1 of 4 treatment groups: placebo; a single 200–400 µg/kg dose of ivermectin (mean 273 µg/kg); 400 mg of albendazole; or albendazole 400 mg with ivermectin 200–400 µg/kg given simultaneously.

Adverse reactions were generally mild and well tolerated, but fever, headache, myalgias, and cough were reported significantly more frequently among children who received ivermectin alone or albendazole and ivermectin combined than among children in the other 2 groups. These reactions may have been due to increased parasite lysis in the ivermectin-treated groups. Severity of symptoms was also significantly greater among children who received ivermectin (with or without albendazole) than among those who received placebo ( $p = 0.005$  and  $p = 0.03$ , respectively). Severity of adverse reactions and microfilarial clearance were similar for children who received low-dose ( $\leq 273$  µg/kg) and high-dose ( $> 273$  µg/kg) ivermectin. No significant differences were found in the frequency or severity of symptoms between children who were treated with ivermectin alone and those who received both ivermectin and albendazole, even among the children who were admitted to hospital.

### 5.2.2.2.1. Safety of 300 µg/kg Dose Administered on 3 Consecutive Days

[Table 12](#) provides a summary of studies that administered a dose of 300 µg/kg ivermectin or higher, and the number of patients exposed.

**Table 12 Extent of Exposure to Ivermectin at Doses of 300 µg and Above**

| Source                                     | Ivermectin Source          | Dose                                                                                                                            | Number Exposed                                                          |
|--------------------------------------------|----------------------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| <a href="#">Addiss et al., 1991</a>        | Merck                      | • 400 µg/kg on day 5                                                                                                            | 10                                                                      |
| <a href="#">Addiss et al., 1993</a>        | Merck                      | • 400 µg/kg x 2, 4 days apart                                                                                                   | 9                                                                       |
| <a href="#">Awadzi et al., 1995</a>        | Merck                      | • 600 µg/kg                                                                                                                     | 24                                                                      |
|                                            |                            | • 800 µg/kg                                                                                                                     | 17                                                                      |
| <a href="#">Awadzi et al., 1999</a>        | Merck                      | • 400–550 µg/kg                                                                                                                 | 25                                                                      |
|                                            |                            | • 600–750 µg/kg                                                                                                                 | 23                                                                      |
|                                            |                            | • 800–950 µg/kg                                                                                                                 | 24                                                                      |
|                                            |                            | • 1600 µg/kg                                                                                                                    | 12                                                                      |
| <a href="#">Bockarie et al., 1998</a>      | Not specified              | • 400 µg/kg with 6 mg/kg DEC                                                                                                    | 1077                                                                    |
| <a href="#">Cartel et al., 1992</a>        | Merck                      | • 400 µg/kg)                                                                                                                    | 37                                                                      |
| <a href="#">Chosidow et al., 2010</a>      | Merck                      | • 400 µg/kg x 2, 7 days apart                                                                                                   | 398                                                                     |
| <a href="#">Cooper et al., 1999</a>        | Not specified              | • 400 µg/kg                                                                                                                     | 8                                                                       |
|                                            |                            | • 600 µg/kg                                                                                                                     | 8                                                                       |
| <a href="#">Dembele et al., 2010</a>       | Merck                      | • 400 µg/kg with 800 mg albendazole x 2 annual doses                                                                            | 19                                                                      |
| <a href="#">Dreyer et al., 1995a</a>       | Not specified              | • 400 µg/kg                                                                                                                     | 11                                                                      |
| <a href="#">Dreyer et al., 1995b</a>       | Not specified              | • 400 µg/kg                                                                                                                     | 15                                                                      |
| <a href="#">Guzzo et al., 2002</a>         | Merck                      | • 30 mg (347–541 mcg/kg)                                                                                                        | 15                                                                      |
|                                            |                            | • 60 mg (713–1091 mcg/kg)                                                                                                       | 12                                                                      |
|                                            |                            | • 90 mg (1031–1466 mcg/kg)                                                                                                      | 12                                                                      |
|                                            |                            | • 120 mg (1404–2000 mcg/kg)                                                                                                     | 12                                                                      |
| <a href="#">Heukelbach et al., 2004</a>    | Solvay Farma S.A. (Brazil) | • 300 µg/kg x2 1 day apart                                                                                                      | 27                                                                      |
| <a href="#">Ismail et al., 2001</a>        | Merck                      | • 400 µg/kg with 600 mg albendazole                                                                                             | 15                                                                      |
| <a href="#">Ismail et al., 1998</a>        | Merck                      | • 400 µg/kg with 600 mg albendazole                                                                                             | 13                                                                      |
|                                            |                            | • 400 µg/kg with 6 mg/kg DEC                                                                                                    | 12                                                                      |
| <a href="#">Kamgno et al., 2004</a>        | Merck                      | • 1 x 400 µg/kg (Year 1) then 800 µg/kg (Year 2 and 3), annually<br>• 2 x 400 µg/kg then 10 x 800 µg/kg, administered 3-monthly | ~286 patients:<br>• 475 doses of 400 µg/kg<br>• 1728 doses of 800 µg/kg |
| <a href="#">Kazura et al., 1993</a>        | Merck                      | • 400 µg/kg                                                                                                                     | 10                                                                      |
| <a href="#">Martin-Prevel et al., 1993</a> | Merck                      | • 300 µg/kg                                                                                                                     | 16                                                                      |
|                                            |                            | • 400 µg/kg                                                                                                                     | 15                                                                      |
| <a href="#">Moulia-Pelat et al., 1996</a>  | Merck                      | • 400 µg/kg x 3 annual doses                                                                                                    | 19                                                                      |
|                                            |                            | • 400 µg/kg with 6 mg/kg DEC x 3 annual doses                                                                                   | 19                                                                      |

**Table 12 Extent of Exposure to Ivermectin at Doses of 300 µg and Above**

| Source                                      | Ivermectin Source                                                    | Dose                                   | Number Exposed |
|---------------------------------------------|----------------------------------------------------------------------|----------------------------------------|----------------|
| <a href="#">Muñoz et al., 2018</a>          | Liconsa Laboratories (Spain)/ Abbott Laboratories (Brazil) Revectina | • 18 mg then 36 mg then 12–24 mg       | 57             |
| <a href="#">Nguyen et al., 1996</a>         | Merck                                                                | • 400 µg/kg x 3 doses 6 months apart   | 872            |
| <a href="#">Ramaiah et al., 2007</a>        | Not specified                                                        | • 400 µg/kg                            | 8526           |
| <a href="#">Smit et al., 2018</a>           | Elea Laboratories (Argentina)                                        | • 300 µg/kg<br>• 600 µg/kg             | 48<br>47       |
| <a href="#">Suputtamongkol et al., 2021</a> | Atlantic Laboratory Ltd. (Thailand)                                  | • 400 µg/kg x2 or x3<br>• 400 µg/kg x3 | 38; 34<br>101  |
| <a href="#">van den Enden et al., 1993</a>  | Not specified                                                        | • 600 µg/kg                            | 7              |
| <b>Total Number Exposed</b>                 |                                                                      |                                        | <b>11,893</b>  |

DEC = diethylcarbamazine

Only one study was conducted that supported a daily repeat-dose regimen ([Smit et al., 2018](#); [Smit et al., 2019](#)). The remaining studies were single-dose or administered annually, at 1- or 3-month intervals or several days apart.

### **Smit 2019**

The Smit study evaluated the PK: PD relationship ([Smit et al., 2019](#)) and the safety, tolerability, and mosquitocidal efficacy ([Smit et al., 2018](#)) between a 3-daily course of ivermectin at doses of 300 µg/kg or 600 µg/kg, co-administered with a standard malaria treatment, dihydroartemisinin-piperaquine (DP). The study enrolled subjects with symptomatic uncomplicated malaria for reasons of recruitment and compliance.

Five (11%) of 45 patients receiving ivermectin 600 mcg/kg per day, two (4%) of 48 patients receiving ivermectin 300 µg/kg per day, and none of 46 patients receiving placebo had one or more treatment-related adverse events.

Two serious adverse events were reported: one QT prolongation of 510 milliseconds with T-wave inversion in the ivermectin 300 µg/kg per day group and one anaphylactic reaction, probably to piperaquine or ivermectin, in the ivermectin 600 µg/kg per day group. Treatment was discontinued for the patient with anaphylactic reaction.

The highest dose (600 µg/kg per day) ivermectin recipients had more adverse events than did those who received placebo. Treatment-related adverse events showed evidence of a dose-response, predominantly reflecting transient minor visual disturbances. All adverse

events were non-severe (grade  $\leq 2$ ), except for 3 patients with pre-existing liver enzyme elevations (two at grade 1 and one at grade 3) who showed grade 3 elevations after treatment.

Maximum change from baseline in QTcF interval (on day 2 + 4 hours), pupil diameter, aspartate aminotransferase values, alanine aminotransferase values (during follow-up), and malaria recurrence did not differ between treatment groups. There was a greater reduction in hemoglobin in the ivermectin 600  $\mu\text{g/kg}$  per day group than in the placebo group, but not in the 300  $\mu\text{g/kg}$  per day group versus placebo (Smit et al., 2018).

It is not known if the findings of good tolerability for the ivermectin regimens in this study are applicable to individuals that are not infected with malaria, are asymptomatic, or individuals infected with SARS-CoV-2.

#### 5.2.2.2.2. Safety of 400 $\mu\text{g/kg}$ Administration

A summary of the exposure to 400  $\mu\text{g/kg}$  ivermectin is provided in Table 13.

**Table 13 Extent of Exposure to Ivermectin at Doses of 400  $\mu\text{g/kg}$  and Above**

| Source                                | Ivermectin Source | Dose                                                                                                               | Number Exposed       |
|---------------------------------------|-------------------|--------------------------------------------------------------------------------------------------------------------|----------------------|
| <a href="#">Addiss et al., 1991</a>   | Merck             | • 400 $\mu\text{g/kg}$ on day 5                                                                                    | 10                   |
| <a href="#">Addiss et al., 1993</a>   | Merck             | • 400 $\mu\text{g/kg}$ x 2, 4 days apart                                                                           | 9                    |
| <a href="#">Awadzi et al., 1995</a>   | Merck             | • 600 $\mu\text{g/kg}$<br>• 800 $\mu\text{g/kg}$                                                                   | 24<br>17             |
| <a href="#">Awadzi et al., 1999</a>   | Merck             | • 400–550 $\mu\text{g/kg}$<br>• 600–750 $\mu\text{g/kg}$<br>• 800–950 $\mu\text{g/kg}$<br>• 1600 $\mu\text{g/kg}$  | 25<br>23<br>24<br>12 |
| <a href="#">Bockarie et al., 1998</a> | Not specified     | • 400 $\mu\text{g/kg}$ with 6 mg/kg DEC                                                                            | 1077                 |
| <a href="#">Cartel et al., 1992</a>   | Merck             | • 400 $\mu\text{g/kg}$                                                                                             | 37                   |
| <a href="#">Chosidow et al., 2010</a> | Merck             | • 400 $\mu\text{g/kg}$ x 2, 7 days apart                                                                           | 398                  |
| <a href="#">Cooper et al., 1999</a>   | Not specified     | • 400 $\mu\text{g/kg}$<br>• 600 $\mu\text{g/kg}$                                                                   | 8<br>8               |
| <a href="#">Dembele et al., 2010</a>  | Merck             | • 400 $\mu\text{g/kg}$ with 800 mg albendazole x 2 annual doses                                                    | 19                   |
| <a href="#">Dreyer et al., 1995a</a>  | Not specified     | • 400 $\mu\text{g/kg}$                                                                                             | 11                   |
| <a href="#">Dreyer et al., 1995b</a>  | Not specified     | • 400 $\mu\text{g/kg}$                                                                                             | 15                   |
| <a href="#">Guzzo et al., 2002</a>    | Merck             | • 30 mg (347–541 mcg/kg)<br>• 60 mg (713–1091 mcg/kg)<br>• 90 mg (1031–1466 mcg/kg)<br>• 120 mg (1404–2000 mcg/kg) | 15<br>12<br>12<br>12 |
| <a href="#">Ismail et al., 2001</a>   | Merck             | • 400 $\mu\text{g/kg}$ with 600 mg albendazole                                                                     | 15                   |
| <a href="#">Ismail et al., 1998</a>   | Merck             | • 400 $\mu\text{g/kg}$ with 600 mg albendazole                                                                     | 13                   |

**Table 13 Extent of Exposure to Ivermectin at Doses of 400 µg/kg and Above**

| Source | Ivermectin Source | Dose                         | Number Exposed |
|--------|-------------------|------------------------------|----------------|
|        |                   | • 400 µg/kg with 6 mg/kg DEC | 12             |

**Table 13 Extent of Exposure to Ivermectin at Doses of 400 µg/kg and Above**

| Source                                             | Ivermectin Source                                                    | Dose                                                                                                                                                                                    | Number Exposed                                                                                                                               |
|----------------------------------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| <a href="#">Kamgno et al., 2004</a>                | Merck                                                                | <ul style="list-style-type: none"> <li>• 1 x 400 µg/kg (Year 1) then 800 µg/kg (Year 2 and 3), annually</li> <li>• 2 x 400 µg/kg then 10 x 800 µg/kg, administered 3-monthly</li> </ul> | ~286 patients administered:<br><ul style="list-style-type: none"> <li>• 475 doses of 400 µg/kg</li> <li>• 1728 doses of 800 µg/kg</li> </ul> |
| <a href="#">Kazura et al., 1993</a>                | Merck                                                                | • 400 µg/kg                                                                                                                                                                             | 10                                                                                                                                           |
| <a href="#">Martin-Prevel et al., 1993</a>         | Merck                                                                | • 400 µg/kg                                                                                                                                                                             | 15                                                                                                                                           |
| <a href="#">Moulia-Pelat et al., 1996</a>          | Merck                                                                | <ul style="list-style-type: none"> <li>• 400 µg/kg x 3 annual doses</li> <li>• 400 µg/kg with 6 mg/kg DEC x 3 annual doses</li> </ul>                                                   | 19<br>19                                                                                                                                     |
| <a href="#">Muñoz et al., 2018</a>                 | Liconsa Laboratories (Spain)/ Abbott Laboratories (Brazil) Revectina | • 18 mg then 36 mg then 12–24 mg                                                                                                                                                        | 57                                                                                                                                           |
| <a href="#">Nguyen et al., 1996</a>                | Merck                                                                | • 400 µg/kg x3 doses 6 months apart                                                                                                                                                     | 872                                                                                                                                          |
| <a href="#">Ramaiah et al., 2007</a>               | Not specified                                                        | • 400 µg/kg                                                                                                                                                                             | 8526                                                                                                                                         |
| <a href="#">Smit et al., 2018</a>                  | Elea Laboratories (Argentina)                                        | • 600 µg/kg                                                                                                                                                                             | 47                                                                                                                                           |
| <a href="#">Suputtamongkol et al., 2021</a>        | Atlantic Laboratory Ltd. (Thailand)                                  | <ul style="list-style-type: none"> <li>• 400 µg/kg x2 or x3</li> <li>• 400 µg/kg x3</li> </ul>                                                                                          | 38; 34<br>101                                                                                                                                |
| <a href="#">van den Enden et al., 1993</a>         | Not specified                                                        | • 600 µg/kg                                                                                                                                                                             | 7                                                                                                                                            |
| <b>Total Number Exposed to 400 µg/kg or Higher</b> |                                                                      |                                                                                                                                                                                         | <b>11,839</b>                                                                                                                                |

DEC = diethylcarbamazine

A large number of patients have been administered a 400 µg/kg ivermectin with relatively few transient adverse events.

#### 5.2.2.2.3. Safety of 600 µg/kg Administered on 3 Consecutive Days

A summary of all patients exposed to 600 µg/kg ivermectin for which safety data are available is provided in [Table 14](#).

**Table 14 Extent of Exposure to Ivermectin at Doses of 600 µg/kg and Above**

| Source                                     | Ivermectin Source                                                     | Dose                                    | Number Exposed                       |
|--------------------------------------------|-----------------------------------------------------------------------|-----------------------------------------|--------------------------------------|
| <a href="#">Awadzi et al., 1995</a>        | Merck                                                                 | • 600 µg/kg                             | 24                                   |
|                                            |                                                                       | • 800 µg/kg                             | 17                                   |
| <a href="#">Awadzi et al., 1999</a>        | Merck                                                                 | • 600–750 µg/kg                         | 23                                   |
|                                            |                                                                       | • 800–950 µg/kg                         | 24                                   |
|                                            |                                                                       | • 1600 µg/kg                            | 12                                   |
| <a href="#">Cooper et al., 1999</a>        | Not specified                                                         | • 600 µg/kg                             | 8                                    |
| <a href="#">Guzzo et al., 2002</a>         | Merck                                                                 | • 60 mg                                 | 12                                   |
|                                            |                                                                       | • 90 mg                                 | 12                                   |
|                                            |                                                                       | • 120 mg                                | 12                                   |
| <a href="#">Kamgno et al., 2004</a>        | Merck                                                                 | • 800 µg/kg x 2 annually                | 1728 doses given to<br>~286 patients |
|                                            |                                                                       | • 800 µg/kg x 10 at 3-monthly intervals |                                      |
| <a href="#">Muñoz et al., 2018</a>         | Liconsal Laboratories (Spain)/ Abbott Laboratories (Brazil) Revectina | • 36 mg                                 | 57                                   |
| <a href="#">Smit et al., 2018</a>          | Elea Laboratories (Argentina)                                         | • 600 µg/kg                             | 47                                   |
| <a href="#">van den Enden et al., 1993</a> | Not specified                                                         | • 600 µg/kg                             | 7                                    |
| <b>Total Number Exposed</b>                |                                                                       |                                         | <b>541</b>                           |

NOTE: 600 mcg/kg dose = 36 mg in a 60-kg adult

DEC = diethylcarbamazine

Similar to the 300 µg/kg dose administered on 3 consecutive days, a single trial ([Smit et al., 2018](#)) is the only study identified to support this dosage regimen. While 541 subjects have been exposed to a single 600 µg/kg dose of ivermectin, there are 47 patients exposed to the daily dosing regimen.

### 5.3. Marketing Experience

#### 5.3.1. Postmarketing Safety Information

The following post-marketing safety information for ivermectin (*italicized*) is provided in the drug product labeling from Edenbridge Pharmaceuticals, LLC ([Edenbridge, 2014](#)) and is applicable to all approved ivermectin products:

##### *Post-Marketing Experience*

*The following adverse reactions have been reported since the drug was registered overseas:*

*Onchocerciasis*

*Conjunctival hemorrhage*

*All Indications*

*Hypotension (mainly orthostatic hypotension), worsening of bronchial asthma, toxic epidermal necrolysis, Stevens-Johnson syndrome, seizures, hepatitis, elevation of liver enzymes, and elevation of bilirubin.*

### **Drug Interactions**

*Post-marketing reports of increased INR (International Normalized Ratio) have been rarely reported when ivermectin was co-administered with warfarin.*

## **5.4. Reference Safety Information**

| <b>System Class</b>      | <b>Organ</b> | <b>Preferred Term</b>                           | <b>Studied Indication</b> | <b>Frequency</b> | <b>Severity</b> |
|--------------------------|--------------|-------------------------------------------------|---------------------------|------------------|-----------------|
| Cardiac Disorders        |              |                                                 |                           |                  |                 |
|                          |              | Facial Edema                                    | Onchocerciasis            | Common           | Non-serious     |
|                          |              | Peripheral Edema                                | Onchocerciasis            | Common           | Non-serious     |
|                          |              | Orthostatic Hypotension/Postural Hypotension    | Onchocerciasis            | Common           | Non-serious     |
|                          |              |                                                 | Microfilaremia            | Not known        | Non-serious     |
|                          |              | Tachycardia                                     | Onchocerciasis            | Common           | Non-serious     |
|                          |              | Hypotension (including orthostatic hypotension) | Postmarketing             | Not known        | Non-serious     |
| Nervous System Disorders |              |                                                 |                           |                  |                 |
|                          |              | Headache                                        | Onchocerciasis            | Uncommon         | Non-serious     |
|                          |              |                                                 | Microfilaremia            | Not known        | Non-serious     |
|                          |              |                                                 | Scabies                   | Uncommon         | Non-serious     |
|                          |              |                                                 | -                         | Not known        | Non-serious     |
|                          |              | Myalgia                                         | Onchocerciasis            | Uncommon         | Non-serious     |
|                          |              |                                                 | Microfilaremia            | Not known        | Non-serious     |
|                          |              | Dizziness                                       | Strongyloidiasis          | Common           | Non-serious     |

| System Class                                    | Organ | Preferred Term      | Studied Indication | Frequency | Severity    |
|-------------------------------------------------|-------|---------------------|--------------------|-----------|-------------|
|                                                 |       |                     | Scabies            | Uncommon  | Non-serious |
|                                                 |       |                     | -                  | Not known | Non-serious |
|                                                 |       | Somnolence          | Strongyloidiasis   | Uncommon  | Non-serious |
|                                                 |       |                     | -                  | Not known | Non-serious |
|                                                 |       | Vertigo             | Strongyloidiasis   | Uncommon  | Non-serious |
|                                                 |       |                     | Microfilaremia     | Not known | Non-serious |
|                                                 |       |                     | -                  | Not known | Non-serious |
|                                                 |       | Tremor              | Strongyloidiasis   | Uncommon  | Serious     |
|                                                 |       |                     | -                  | Not known | Serious     |
|                                                 |       | Seizures            | Postmarketing      | Not known | Serious     |
|                                                 |       |                     | -                  | Not known | Serious     |
|                                                 |       | Difficulty Focusing | -                  | Not known | Non-serious |
|                                                 |       | Confusion           | -                  | Not known | Non-serious |
| Musculoskeletal and Connective Tissue Disorders |       | Asthenia/Fatigue    | Strongyloidiasis   | Uncommon  | Non-serious |
|                                                 |       |                     | Microfilaremia     | Not known | Non-serious |
|                                                 |       |                     | -                  | Not known | Non-serious |
|                                                 |       | Arthralgia          | Scabies            | Uncommon  | Non-serious |
|                                                 |       |                     | Microfilaremia     | Not known | Non-serious |
|                                                 |       | Lethargy            | Scabies            | Uncommon  | Non-serious |
|                                                 |       | Listlessness        | Scabies            | Uncommon  | Non-serious |
|                                                 |       | Weakness            | Microfilaremia     | Not known | Non-serious |
|                                                 |       | Muscle Pain         | -                  | Not known | Non-serious |
|                                                 |       |                     |                    |           |             |

| System Class                           | Organ | Preferred Term                                                  | Studied Indication | Frequency | Severity    |
|----------------------------------------|-------|-----------------------------------------------------------------|--------------------|-----------|-------------|
| Gastrointestinal Disorders             |       | Abdominal Pain/Discomfort                                       | Strongyloidiasis   | Uncommon  | Non-serious |
|                                        |       |                                                                 | Scabies            | Uncommon  | Non-serious |
|                                        |       |                                                                 | -                  | Not known | Non-serious |
|                                        |       | Anorexia                                                        | Strongyloidiasis   | Uncommon  | Non-serious |
|                                        |       |                                                                 | Scabies            | Uncommon  | Non-serious |
|                                        |       | Constipation                                                    | Strongyloidiasis   | Uncommon  | Non-serious |
|                                        |       | Diarrhea                                                        | Strongyloidiasis   | Common    | Non-serious |
|                                        |       |                                                                 | -                  | Not known | Non-serious |
|                                        |       | Nausea                                                          | Strongyloidiasis   | Common    | Non-serious |
|                                        |       |                                                                 | -                  | Not known | Non-serious |
|                                        |       | Vomiting                                                        | Strongyloidiasis   | Uncommon  | Non-serious |
|                                        |       |                                                                 | -                  | Not known | Non-serious |
|                                        |       | Digestive Disorders (anorexia, abdominal pain, epigastric pain) | Microfilaremia     | Not known | Non-serious |
|                                        |       | Lack of Appetite                                                | -                  | Not known | Non-serious |
| Skin and Subcutaneous Tissue Disorders |       |                                                                 |                    |           |             |
|                                        |       | Pruritus                                                        | Strongyloidiasis   | Common    | Non-serious |
|                                        |       |                                                                 | Scabies            | Common    | Non-serious |
|                                        |       |                                                                 | -                  | Not known | Non-serious |
|                                        |       | Rash                                                            | Strongyloidiasis   | Uncommon  | Non-serious |
|                                        |       |                                                                 | Scabies            | Uncommon  | Non-serious |
|                                        |       |                                                                 | -                  | Not known | Non-serious |

| <b>System Class</b>                                  | <b>Organ</b> | <b>Preferred Term</b>         | <b>Studied Indication</b> | <b>Frequency</b> | <b>Severity</b> |
|------------------------------------------------------|--------------|-------------------------------|---------------------------|------------------|-----------------|
|                                                      |              | Urticaria                     | Strongyloidiasis          | Uncommon         | Non-serious     |
|                                                      |              | Toxic Epidermal Necrolysis    | Postmarketing             | Not known        | Serious         |
|                                                      |              | Stevens-Johnson Syndrome      | Postmarketing             | Not known        | Serious         |
| General Disorders and Administration Site Conditions |              |                               |                           |                  |                 |
|                                                      |              | Fever                         | Microfilaremia            | Not known        | Non-serious     |
|                                                      |              | Body Pain                     | Microfilaremia            | Not known        | Non-serious     |
|                                                      |              | Cough                         | Microfilaremia            | Not known        | Non-serious     |
|                                                      |              | Sore Throat                   | Microfilaremia            | Not known        | Non-serious     |
|                                                      |              | Chills                        | Microfilaremia            | Not known        | Non-serious     |
|                                                      |              | Diaphoresis                   | Microfilaremia            | Not known        | Non-serious     |
|                                                      |              | General Malaise               | -                         | Not known        | Non-serious     |
| Respiratory, Thoracic and Mediastinal Disorders      |              |                               |                           |                  |                 |
|                                                      |              | Respiratory Discomfort        | Microfilaremia            | Not known        | Non-serious     |
|                                                      |              | Worsening of Bronchial Asthma | Postmarketing             | Not known        | Serious         |
| Reproductive System and Breast Disorders             |              |                               |                           |                  |                 |
|                                                      |              | Testicular Pain or Discomfort | Microfilaremia            | Not known        | Non-serious     |
| Blood and Lymphatic System Disorders                 |              |                               |                           |                  |                 |
|                                                      |              | Eosinophilia                  | Onchocerciasis            | Common           | Non-serious     |
|                                                      |              | Hemoglobin Increase           | Onchocerciasis            | Common           | Non-serious     |
|                                                      |              | Elevation of ALT and/or AST   | Strongyloidiasis          | Common           | Non-serious     |
|                                                      |              | Decrease in Leukocyte Count   | Strongyloidiasis          | Common           | Non-serious     |
|                                                      |              | Leukopenia                    | Strongyloidiasis          | Common           | Non-serious     |
|                                                      |              | Anemia                        | Strongyloidiasis          | Common           | Non-serious     |

| System Class            | Organ | Preferred Term                                  | Studied Indication | Frequency | Severity    |
|-------------------------|-------|-------------------------------------------------|--------------------|-----------|-------------|
|                         |       | Elevation of Liver Enzymes                      | Postmarketing      | Not known | Non-serious |
|                         |       | Elevation of Bilirubin                          | Postmarketing      | Not known | Non-serious |
|                         |       | Prolonged Activated Partial Thromboplastic Time | -                  | Not known | Non-serious |
| Hepatobiliary Disorders |       |                                                 |                    |           |             |
|                         |       | Hepatitis                                       | Postmarketing      | Not known | Serious     |
| Eye Disorders           |       |                                                 |                    |           |             |
|                         |       | Blurred Vision                                  | -                  | Not known | Non-serious |
|                         |       | Difficulty Reading                              | -                  | Not known | Non-serious |
|                         |       | Tunnel Vision                                   | -                  | Not known | Non-serious |
|                         |       | Floaters                                        | -                  | Not known | Non-serious |
|                         |       | Black Spots                                     | -                  | Not known | Non-serious |
|                         |       | Abnormal Colors or Shapes                       | -                  | Not known | Non-serious |

## 6. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATION

The information in the following sections was adapted from the labeling for approved oral ivermectin products ([Merck, 2009](#); [Edenbridge, 2014](#); [Merck Sharp & Dohme, 2014](#); [Merck Sharp & Dohme BV, 2015](#)) and information from the literature cited in sections above.

Please also refer to the approved product labeling provided in the [Appendix](#).

### 6.1. Indication

The proposed indication is for the treatment of COVID-19 in patients aged 18 and over with certain comorbidities, or with shortness of breath as part of their COVID-19 illness, and those aged 65 and over, with confirmed or possible COVID-19 who meet the current case definition for possible COVID-19, and who are well enough to remain in the community. Onset of symptoms or a positive test for SARS-Co-V2 infection with symptoms of COVID-19 must be within the last 14 days.

## **6.2. Dosage and Administration**

Study drug is to be administered orally according to the dosage specified in the study protocol. The study drug should be taken should be taken on an empty stomach with water.

## **6.3 How Supplied**

Product will be supplied in unit dose packages of 20 tablets and will be stored according to the product labeling (refer to the product labeling in the [Appendix](#)). For the clinical study, an independent team will label the packages as shows in [Figure 4](#).

**Figure 4 Investigational Labeling for Oral Ivermectin**

|                      |                 |
|----------------------|-----------------|
| Study Title          | PRINCIPLE       |
| EudraCT No           | 2020-001209-22  |
| Version Number, Date | V1.0 15.03.2021 |

| Description of information needed                                                                                                                               | Label Text                                                                                                                                                                                  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Name, address, and telephone number of the sponsor</b><br>(the main contact for information on the product, clinical trial, and emergency unblinding)        | University of Oxford<br>Joint Research Office<br>1st floor, Boundary Brook House<br>Churchill Drive,<br>Headington<br>Oxford<br>OX3 7GB<br>Tel: +44 (0)1865572224<br>Fax: +44 (0)1865572228 |
| <b>Pharmaceutical dosage form, route of administration, quantity of dosage units,</b> and in the case of open trials, the name/identifier and strength/potency; | Ivermectin (3 mg) tablets<br><br>The capsules are for oral administration.                                                                                                                  |
| <b>Batch and/or code number</b> to identify the contents and packaging operation;                                                                               |                                                                                                                                                                                             |
| <b>Trial reference code</b> allowing identification of the <u>trial, site, investigator and sponsor</u> if not given elsewhere;                                 | PRINCIPLE trial.<br>University of Oxford<br>Chief Investigator: Prof. Chris Butler                                                                                                          |
| <b>Trial subject identification number</b> /treatment number and where relevant, the visit number;                                                              |                                                                                                                                                                                             |
| <b>Kit/Pack number</b>                                                                                                                                          |                                                                                                                                                                                             |
| <b>Investigator</b> (if not included previously)                                                                                                                |                                                                                                                                                                                             |

|                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Directions for use</b><br/>         (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product)</p> | <p>Ivermectin 3mg tablets.</p> <p>Dosage is dependent on body weight -</p> <p><b>45-64 kg: Take a single dose of 18mg (6 tablets) each day for three days (18 tablets in total)</b><br/> <b>65-84 kg: Take a single dose of 24 mg (8 tablets) each day for three days (24 tablets in total)</b><br/> <b>≥84 kg: Take a single dose of 30mg (10 tablets) each day for 3 days (30 tablets in total).</b></p> <p>Please return any remaining tablets to the trial team.</p> <p>Special instructions:<br/>         You should take the daily number of tablets in one dose. The dose may be taken at any time of the day, but no food should be taken within two hours before or after administration.</p> |
| <p><b>“For clinical trial use only”</b> or similar wording;</p>                                                                                                                     | <p>For clinical trial use only</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <p><b>Storage conditions</b></p>                                                                                                                                                    | <p>Store below 30°C</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p><b>Period of use</b><br/>         (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity</p>                   | <p>3 days</p> <p>Expiry date: month/year</p> <p>Shelf life is xx.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

|                                                                                                                                     |                               |
|-------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| <b>“keep out of reach of children”</b> except when the product is for use in trials where the product is not taken home by subjects | Keep out of reach of children |
|-------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|

## 6.4 Contraindications

The study drug is contraindicated in patients who are hypersensitive to ivermectin or any component of this product.

## 6.5 Warnings/Precautions

### Microfilaricidal Drugs

Concomitant treatment with microfilaricidal drugs, such as diethylcarbamazine citrate (DEC) and ivermectin in mass chemotherapy campaigns for onchocerciasis or filariasis caused by *Wuchereria bancrofti* in Africa is not recommended.

Historical data have shown that microfilaricidal drugs such as DEC might cause cutaneous and/or systemic reactions of varying severity (the Mazzotti-type reaction) and ophthalmological reactions in patients with onchocerciasis. These reactions are probably due to allergic and inflammatory responses to the death of microfilariae, and the intensity and severity of adverse experiences are probably related to the pretreatment microfilarial density particularly in the blood. Patients treated with ivermectin for onchocerciasis may experience these reactions in addition to clinical adverse reactions possibly, probably, or definitely related to the drug itself.

The treatment of severe Mazzotti reactions has not been subjected to controlled clinical trials. Oral hydration, recumbency, intravenous normal saline, and/or parenteral corticosteroids have been used to treat postural hypotension. Antihistamines and/or aspirin have been used for most mild to moderate cases.

Rarely, patients with onchocerciasis who are also heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide. In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival hemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma. This syndrome has been seen very rarely following the use of ivermectin. In individuals who warrant treatment with ivermectin for any reason and have had significant exposure to *Loa loa*-endemic areas of West or Central Africa, pretreatment assessment for loiasis and careful post-treatment follow-up should be implemented.

After treatment with microfilaricidal drugs, patients with hyperreactive onchodermatitis (sowda) may be more likely than others to experience severe adverse reactions, especially edema and aggravation of onchodermatitis.

Please also refer to the approved product labeling provided in the [Appendix](#).

## 6.6 Drug Interactions

### Inhibitors of CYP3A or P-glycoprotein

The findings of *in vitro* studies using human liver microsomes suggest that clinically relevant concentrations of ivermectin do not significantly inhibit the metabolizing activities of CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2E1.

Ivermectin is metabolized by CYP3A enzymes and transported across the blood-brain barriers by the drug transporter P-glycoprotein (P-gp, ABCB1). Due to extensive polymorphism in CYP3A5 phenotypes in African populations, ivermectin should not be co-administered with the drugs shown below because they may increase ivermectin exposure by inhibiting its metabolism and excretion or competing with CYP enzymes or P-gp ([Table 155](#)):

**Table 15 Drugs that Should Not Be Co-administered With Ivermectin**

| Class                            | Drug                                                                |
|----------------------------------|---------------------------------------------------------------------|
| Antiarrhythmic/ Antihypertensive | Quinidine<br>Amiodarone<br>Diltiazem<br>Spironolactone<br>Verapamil |
| Antibiotic- Macrolides           | Clarithromycin<br>Erythromycin                                      |
| Antifungal agents                | Itraconazole<br>Ketoconazole                                        |
| Immunosuppressants               | Cyclosporine<br>Tacrolimus                                          |
| Anti HIV therapy                 | Indinavir<br>Ritonavir                                              |

### Microfilaricidal Drugs

Concomitant treatment with diethylcarbamazine citrate (DEC) and ivermectin in mass chemotherapy campaigns for onchocerciasis or for filariasis caused by *Wuchereria bancrofti* in Africa is not recommended. See also Section 6.5.

### Warfarin

Post-marketing reports of increased INR (International Normalized Ratio) have been rarely reported when ivermectin was co-administered with warfarin.

## 6.7 Usage in Pregnancy

At high doses, ivermectin has been shown to be teratogenic in mice, rats, and rabbits. Teratogenicity was characterized in the three species tested by cleft palate; clubbed forepaws were additionally observed in rabbits. These developmental effects were found only at or near

doses that were maternotoxic to the pregnant female. Therefore, ivermectin does not appear to be selectively fetotoxic to the developing fetus. There are, however, no adequate and well-controlled studies in pregnant women. Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.

Women of childbearing age will be asked about their pregnancy status and pregnancy tests will be performed privately before any dose with study product. If the test is positive or rejected, or if the woman is visibly pregnant, the woman will be excluded from clinical trials. To minimize the risk of social harm, assent will be administered privately prior to drug administration regardless of the gender of the minor. This is to maintain participant confidentiality while at the same time avoiding singling out the female minors and the requirement for pregnancy tests. Pregnancy results for minors will not be disclosed to parents or legal guardians.

### **6.8 Nursing Mothers**

Ivermectin is excreted in human milk in low concentrations. Ivermectin should not be administered to lactating women < 1 week postpartum.

### **6.9 Usage in Pediatrics**

Safety in pediatric subjects < 15 kg has not been established. Ivermectin should not be administered to subjects < 15 kg.

### **6.10 Impaired Renal or Hepatic Function**

Ivermectin has not been studied in patients with impaired hepatic function or impaired renal function. As ivermectin is extensively metabolized by the liver, caution should be exercised if ivermectin is administered to patients with impaired hepatic function.

### **6.11 Adverse Reactions**

#### **Onchocerciasis**

In clinical trials involving 963 adult patients who received 100 to 200 mcg/kg ivermectin, the following clinical adverse reactions were reported as possibly, probably, or definitely related to the drug in  $\geq 1\%$  of the patients:

- facial edema 1.2%
- peripheral edema 3.2%
- orthostatic hypotension 1.1%
- and tachycardia 3.5%

Drug-related headache and myalgia occurred in < 1% of patients (0.2% and 0.4%, respectively). However, these were the most common adverse experiences reported overall during these trials regardless of causality (22.3% and 19.7%, respectively).

A similar safety profile was observed in an open study in pediatric patients ages 6 to 13 years.

### **Strongyloidiasis**

In 4 clinical studies involving a total of 109 patients given either one or two doses of 170 to 200 mcg/kg of ivermectin, the following adverse reactions were reported as possibly, probably, or definitely related to ivermectin:

- Body as a Whole
  - asthenia/fatigue 0.9%
  - abdominal pain 0.9%
- Gastrointestinal
  - anorexia 0.9%
  - constipation 0.9%
  - diarrhea 1.8%
  - nausea 1.8%
  - vomiting 0.9%
- Nervous System/Psychiatric
  - dizziness 2.8%
  - somnolence 0.9%
  - vertigo 0.9%
  - tremor 0.9%
- Skin
  - pruritus 2.8%
  - rash 0.9%
  - urticaria 0.9%

### **Scabies**

Adverse effects reported in the literature review were similar to those reported in clinical trials for the other indications. The most common adverse drug reactions reported with ivermectin in the review involved the transient exacerbation of pruritus that can sometimes occur as a result of sensitization of the human host to mite antigens, with a consequent immunologic reaction (1.4%). Sensitization also frequently results in delayed resolution of symptoms. Patients should be warned that itching may persist for one to two weeks after treatment, even if the mite is successfully eradicated.

Other frequently reported reactions consisted of headache (< 1.0%), arthralgia (< 1.0%), and anorexia (< 1.0%). Additionally, lethargy (< 1.0%), listlessness (< 1.0%), abdominal

discomfort (< 1.0%), rash (< 1.0%), and dizziness (< 1.0%) were reported. Up to 1.86% of patients noticed that they had passed *Ascaris* worms during the week after treatment.

### **Microfilaremia**

In the treatment of filariasis caused by *Wuchereria bancrofti*, the intensity of the side effects does not seem to be dose-related but is related to the blood microfilarial density. The following have been reported: fever, headache, asthenia, feeling of weakness, myalgia, arthralgia, body pain, digestive disorders (such as anorexia, nausea, abdominal, and epigastric pain), cough, feeling of respiratory discomfort, sore throat, postural hypotension, chills, vertigo, diaphoresis, testicular pain or feeling of discomfort.

### **Laboratory Test Findings**

In controlled clinical trials in patients with onchocerciasis, the following laboratory adverse experiences were reported as possibly, probably, or definitely related to the drug in  $\geq 1\%$  of the patients: eosinophilia (3%) and hemoglobin increase (1%).

In clinical trials involving 109 patients with strongyloidiasis given either one or two doses of 170 to 200 mcg/kg ivermectin, the following laboratory abnormalities were seen regardless of drug relationship: elevation in ALT and/or AST (2%), decrease in leukocyte count (3%). Leukopenia and anemia were seen in one patient.

### **Post-Marketing Experience**

The following postmarketing adverse reactions have been reported:

#### Onchocerciasis

Conjunctival hemorrhage

#### All Indications

Hypotension (mainly orthostatic hypotension), worsening of bronchial asthma, toxic epidermal necrolysis, Stevens-Johnson syndrome, seizures, hepatitis, elevation of liver enzymes, and elevation of bilirubin.

### **Clinical Trial Adverse Events**

Visual disturbances: blurred vision, difficulty reading, tunnel vision, floaters, black spots, abnormal colors or shapes

CNS: dizziness, tremor, somnolence, vertigo, difficulty focusing, confusion, seizures, headache

Gastrointestinal: diarrhea, nausea, vomiting, abdominal pain, lack of appetite

Skin: rash, pruritus

General: fatigue, general malaise, muscle pain

### **Rare**

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrosis (TEN)

Prolonged activated partial thromboplastic time (aPTT)

## **6.12 Drug Abuse and Dependence**

Ivermectin is not known to be habit forming; the potential for abuse and dependence is very low.

## **6.13 Overdosage**

### **Signs and Symptoms**

Significant lethality was observed in mice and rats after single oral doses of 25 to 50 mg/kg and 40 to 50 mg/kg, respectively. No significant lethality was observed in dogs after single oral doses of up to 10 mg/kg. At these doses, the treatment-related signs that were observed in these animals include ataxia, bradypnea, tremors, ptosis, decreased activity, emesis, and mydriasis.

In accidental intoxication with, or significant exposure to, unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection, or exposure to body surfaces, the following adverse effects have been reported most frequently: rash, edema, headache, dizziness, asthenia, nausea, vomiting, and diarrhea. Other adverse effects that have been reported include: seizure, ataxia, dyspnea, abdominal pain, paresthesia, urticaria, and contact dermatitis.

### **Treatment**

In case of accidental poisoning, 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. Induction of emesis and/or gastric lavage as soon as possible, followed by purgatives and other routine anti-poison measures, may be indicated if needed to prevent absorption of ingested material.

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## 8 APPENDIX

### Drug Product Labeling, Edenbridge Pharmaceuticals, LLC

Manufacturer: Edenbridge (USA), Labelling, QP release: Torbay & South Devon NHS Foundation Trust, trading as Torbay Pharmaceuticals (MHRA site number is 13079)

#### Revision History

| <b>Edition</b> | <b>Change</b>               | <b>Justification</b> | <b>Date</b>    |
|----------------|-----------------------------|----------------------|----------------|
| 1              | New                         | Initial Edition      | April 2, 2021  |
| 2              | Added RSI; revision history | MRHA comment         | April 21, 2021 |