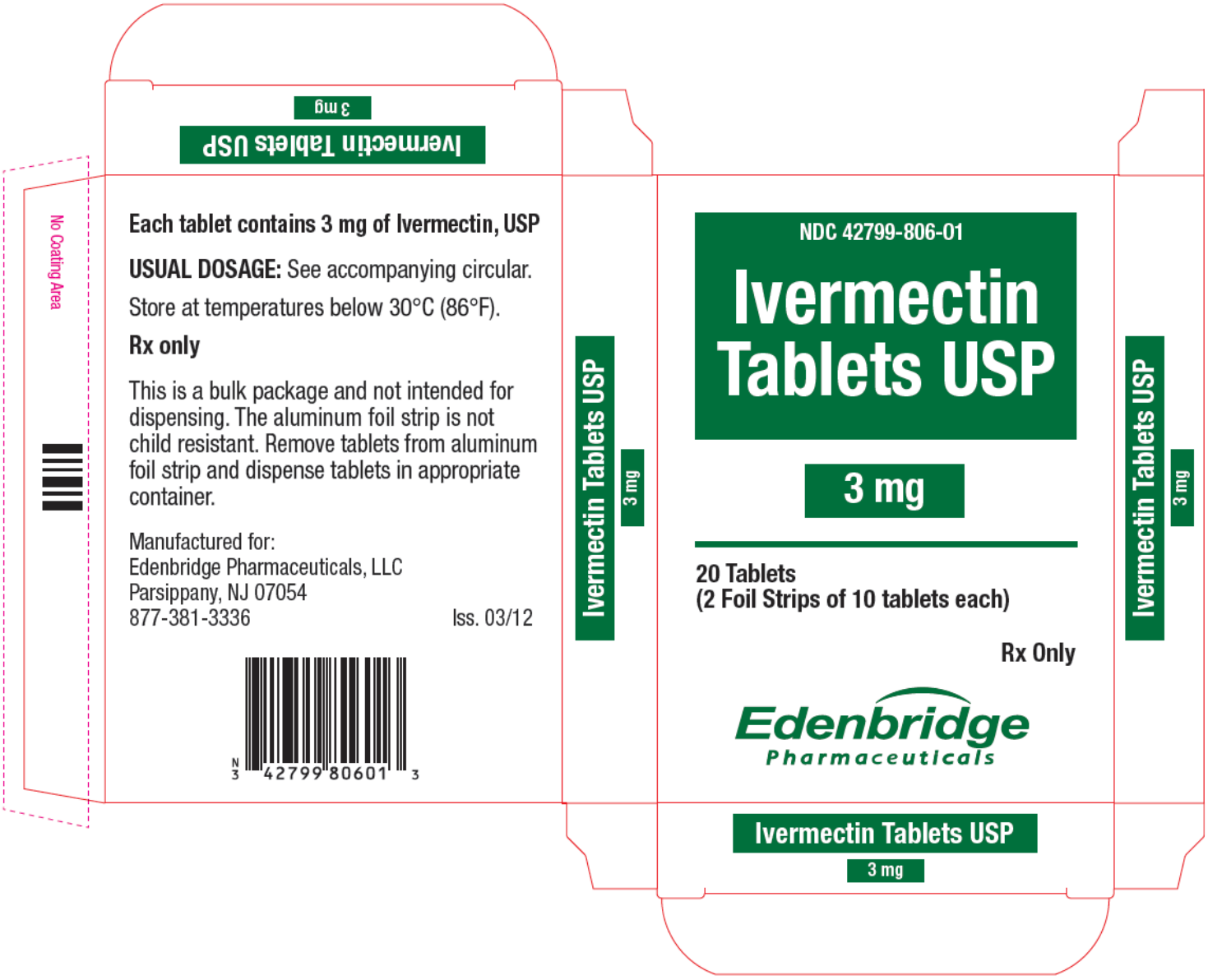
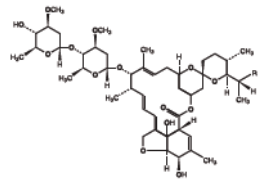
(b) (4)



Ivermectin Tablets USP, 3 mg

DESCRIPTION

Ivermectin is a semisynthetic, antihelmintic 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_{1a} and less than 10% 5-*O*-demethyl-25-(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)avermectin A_{1a}, generally referred to as 22,23-dihydroavermectin B_{1a} and B_{1b}, or H_2B_{1a} and H_2B_{1b}, respectively. The respective empirical formulas are $C_{48}H_{74}O_{14}$ and $C_{47}H_{72}O_{14}$, with molecular weights of 875.10 and 861.07, respectively. The structural formulas are



Component B_{1a}, R = C_2H_5 Component B_{1b}, R = CH_3

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 is soluble in 95% ethanol.

Ivermectin tablets are available as 3 mg tablets containing the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Following oral administration of ivermectin, plasma concentrations are approximately proportional to the dose within 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 48.6 (±21.9) (range: 16.4 to 101.3) and 30.6 (±15.6) (range: 13.9 to 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 entirely 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 ± 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.

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.

Microbiology

Ivermectin is a member of the avermectin class of broad-spectrum antiparasitic agents which have a unique mode of action. Compounds of this 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 ion channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

The selective activity of compounds of this class is attributable in part 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 microfilariae of *Onchocerca volvulus* as well as not against the adult form. Its activity against *Strongyloides stercoralis* is limited to the intestinal stages.

Clinical Studies

Strongyloidiasis

Two controlled clinical studies using albendazole as the comparative agent were carried out in international sites where albendazole is approved for the treatment of strongyloidiasis of the gastrointestinal tract, and three controlled studies were carried out in the U.S. and internationally using albendazole as the comparative agent. Efficacy, as measured by cure rate, was defined as the absence of larvae in at least two follow-up stool examinations 3 to 4 weeks post therapy. Based on this criterion, efficacy was significantly greater for ivermectin tablets (a single dose of 170 to 200 mcg/kg) than for albendazole (200 mg b.i.d. for 3 days). Ivermectin Tablets administered as a single dose of 200 mcg/kg for 1 day was as efficacious as thiabendazole administered at 25 mg/kg b.i.d. for 3 days.

Summary of Cure Rates for Ivermectin Versus Comparator Agents in the Treatment of Strongyloidiasis

	Cure Rate* (%)	
	Ivermectin†	Comparative Agent
Albendazole‡ Comparative		
International Study	24/26 (92)	13/22 (55)
WHO Study	129/152 (83)	67/149 (45)
Thiabendazole§ Comparative		
International Study	9/14 (64)	13/15 (87)
US Studies	14/14 (100)	16/17 (94)

*Number and % of evaluable patients
†170 to 200 mcg/kg
‡200 mg b.i.d. for 3 days
§25 mg/kg b.i.d. for 3 days

In one study conducted in France, a non-endemic area where there was no possibility of reinfection, several patients were observed to have recrudescence of *Strongyloides* larvae in their stool as long as 106 days following Ivermectin therapy. Therefore, at least three stool examinations should be conducted over the three months following treatment to ensure eradication. If recrudescence of larvae is observed, re-treatment with Ivermectin is indicated. Concentration techniques (such as using a Baermann apparatus) should be employed when performing these stool examinations, as the number of *Strongyloides* larvae per gram of feces may be very low.

Onchocerciasis

The evaluation of Ivermectin in the treatment of onchocerciasis is based on the results of clinical studies involving 1770 patients in a double-blind, placebo-controlled study involving adult patients with moderate to severe onchocercal skin disease, which received a single dose of 150 mcg/kg Ivermectin Tablets experienced an 83.2% and 99.5% decrease in skin microfilariae count (geometric mean) 3 days and 3 months after the dose, respectively. A marked reduction of >90% was maintained for up to 12 months after the single dose. As with other microfilaricidal drugs, there was an increase in the microfilariae count in the anterior chamber of the eye at day 3 after treatment in some patients. However, at 3 and 6 months after the dose, a significantly greater percentage of patients treated with Ivermectin had decreases in microfilariae counts in the anterior chamber than patients treated with placebo.

In a separate open study involving pediatric patients ages 6 to 15 (n=103, weight range: 17 to 41 kg), similar decreases in skin microfilariae counts were observed for up to 12 months after dosing.

INDICATIONS AND USAGE

Ivermectin is indicated for the treatment of the following infections:

Strongyloidiasis: The intestinal threadworm, *Strongyloides stercoralis* (i.e., non-disseminated) strongyloidiasis due to the nematode parasite *Strongyloides stercoralis*. This indication is based on clinical studies of both comparative and open-label designs, in which 64-100% of infected patients were cured following a single 200 mcg/kg dose of Ivermectin. (See CLINICAL PHARMACOLOGY, Clinical Studies)

Onchocerciasis: Ivermectin is indicated for the treatment of onchocerciasis due to the nematode parasite *Onchocerca volvulus*.

This indication is based on randomized, double-blind, placebo-controlled and comparative studies conducted in 1427 patients in onchocerciasis-endemic areas of West Africa. The comparative studies used diethylcarbamazine citrate (DEC-C).

NOTE: Ivermectin has no activity against adult *Onchocerca volvulus* parasites. The adult parasites reside in subcutaneous nodules which are infrequently palpable. Surgical excision of these nodules (onchocliectomy) may be considered in the management of patients with onchocerciasis, since this procedure will eliminate the microfilariae-producing adult parasites.

CONTRAINDICATIONS

Ivermectin Tablets are contraindicated in patients who are hypersensitive to any component of this product.

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 (See ADVERSE REACTIONS, Onchocerciasis).

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

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

Rarely, patients with onchocerciasis who are also heavily infected with *Loa loa* may develop 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), headaches, 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 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 *Loa loa* and careful pretreatment follow-up should be long-asserted.

Information for Patients

Ivermectin Tablets should be taken on an empty stomach with water. (See CLINICAL PHARMACOLOGY, Pharmacokinetics)

Strongyloidiasis: The patient should be reminded of the need for repeated stool examinations to document clearance of infection with *Strongyloides stercoralis*.

Onchocerciasis: The patient should be reminded that treatment with Ivermectin does not kill the adult *Onchocerca* parasites, and therefore repeated follow-up and retreatment is usually required.

Drug Interactions
Post-marketing reports of increased INR (International Normalized Ratio) have been received when ivermectin was coadministered with warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ivermectin.

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

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/m²/day basis).

Pregnancy
Teratogenic Effects
Pregnancy Category C
Ivermectin has been shown to be teratogenic in mice, rats, and rabbits when given in repeated doses of 0.2, 0.1, and 4.5 times the maximum recommended human dose, respectively (on a mg/m²/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. These are, ivermectin does not appear to be as actively 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.

Nursing Mothers
Ivermectin is excreted in human milk in low concentrations. Treatment of mothers who intend to breast-feed 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.

Strongyloidiasis in Immunocompromised Hosts
In immunocompromised (including HIV-infected) patients being treated for intestinal strongyloidiasis, repeated courses of therapy may be required. Adequate and well controlled clinical studies have not been conducted in such patients to determine the optimal dosing regimen. Several treatments, i.e., at 2 week intervals, may be required, and cure may not be achievable. Control of extra-intestinal strongyloidiasis in these patients is difficult, and suppressive therapy, i.e., once per month, may be helpful.

ADVERSE REACTIONS
Strongyloidiasis
In four 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%), rumor (0.9%).

Skin: pruritus (2.8%), rash (0.9%), and urticaria (0.9%).

In comparative trials, pruritus resulted with ivermectin appeared more abdominal discomfort and chest discomfort than patients treated with albendazole. However, ivermectin was better tolerated than thiabendazole in comparative studies involving 37 patients treated with thiabendazole.

The Mazzotti-type and ophthalmologic reactions associated with the host-treatment of onchocerciasis or the disease itself would not be expected to occur in strongyloidiasis patients treated with ivermectin. (See ADVERSE REACTIONS, Onchocerciasis)

Laboratory Test Findings
In clinical trials involving 209 patients 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.

Onchocerciasis
In clinical trials involving 563 adult patients treated with 100 to 200 mcg/kg Ivermectin Tablets, worsening of the following Mazzotti reactions during the first 4 days post-treatment was reported: arthralgia/myalgia (9.3%), axillary lymph node enlargement and tenderness (11.0% and 4.4%, respectively), cervical lymph node enlargement and tenderness (5.3% and 2.2%, respectively), inguinal lymph node enlargement and tenderness (12.6% and 13.9%, respectively), other lymph node enlargement and tenderness (3.8% and 1.9%, respectively), pruritus (27.5%), skin involvement including edema, papular and pustular or frank urticarial rash (22.7%), and fever (22.6%). (See WARNINGS)

In clinical trials, ophthalmological conditions were examined in 563 adult patients before treatment, at day 3, and months 3 and 6 after treatment with 100 to 200 mcg/kg Ivermectin. Changes observed were primarily deterioration from baseline 3 days post-treatment. Most changes either returned to baseline condition or improved over baseline severity at the month 3 and 6 visits. The percentages of patients with worsening of the following conditions at day 3, month 3 and 6, respectively, were: keratitis 5.5%, 4.6%, and 3.5%; and punctate opacity 3.8%, 3.8%, and 1.4%. The corresponding percentages for patients treated with placebo were: limited to 1.2%, 0.9%, and 0.4%; and punctate opacity 2.0%, 0.4%, and 0.2%. (See WARNINGS)

In clinical trials involving 563 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 ≥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 cause (22.3% and 19.7%, respectively).

A similar safety profile was observed in an open study in pediatric patients ages 6 to 15.

The following ophthalmological side effects do occur due to the disease itself but have also been reported after treatment with Ivermectin: alterations in the eyes, eyelid edema, anterior uveitis, conjunctivitis, keratitis, and chorioretinitis or choroiditis. These have rarely been severe or associated with loss of vision and have generally resolved without corticosteroid treatment.

Laboratory Test Findings
In controlled clinical trials, the following laboratory adverse experiences were reported as possibly, probably, or definitely related to the drug in ≥1% of the patients: eosinophilia (3%) and hemoglobin increase (1%).

Post-Marketing Experience
The following adverse reactions have been reported since the drug was registered overseas:

Onchocerciasis

Conjunctival hemorrhage

Allergications

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

OVERDOSAGE
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 ataxia 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 on 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: seizures, ataxia, dyspnea, abdominal pain, paresthesia, urticaria, and contact dermatitis.

In cases of accidental poisoning, supportive therapy, if indicated, should include serum and 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 purgative and other routine anti-poison measures, may be indicated. Forced drip-sweat absorption of ingested material.

DOSAGE AND ADMINISTRATION
Strongyloidiasis
The recommended dosage of Ivermectin Tablets for the treatment of strongyloidiasis is as a single oral dose designed to provide approximately 200 mcg of ivermectin per kg of bodyweight. See Table 1 for dosage guidelines. Patients should take tablets on an empty stomach with water (See CLINICAL PHARMACOLOGY, Pharmacokinetics). In general, additional doses are not necessary. However, follow-up stool examinations should be performed to verify eradication of infection (See CLINICAL PHARMACOLOGY, Clinical Studies).

Table 1 Dosage Guidelines for Ivermectin Tablets for Strongyloidiasis

Body Weight (kg)	Single Oral Dose Number of 3 mg Tablets
15 to 24	1 tablet
25 to 35	2 tablets
36 to 50	3 tablets
51 to 65	4 tablets
66 to 79	5 tablets
≥80	200 mcg/kg

Onchocerciasis
The recommended dosage of Ivermectin Tablets for the treatment of onchocerciasis is a single oral dose designed to provide approximately 150 mcg of ivermectin per kg of bodyweight. See Table 2 for dosage guidelines. Patients should take tablets on an empty stomach with water. See CLINICAL PHARMACOLOGY, Pharmacokinetics). In mass distribution campaigns or retreatment 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.

Table 2 Dosage Guidelines for Ivermectin Tablets for Onchocerciasis

Body Weight (kg)	Single Oral Dose Number of 3 mg Tablets
15 to 25	1 tablet
26 to 44	2 tablets
45 to 64	3 tablets
65 to 84	4 tablets
≥85	150 mcg/kg

HOW SUPPLIED
Ivermectin Tablets USP, 3 mg are white, round, flat, bevel-edged tablets debossed with "806" on one side and plain on the other side. They are supplied as follows:

NDC 42799-806-01 unit dose packages of 20

Storage
Store at temperatures below 30° C (86°F).

Manufactured for

Edenbridge Pharmaceuticals LLC
Parsippany, NJ 07054

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