PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

ILADEK 3 (tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 3 mg of ivermectin

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

The tablets are round, white or almost white, flat chamfered and 5,5 mm in diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of gastrointestinal strongyloidiasis (anguillulosis).
- Treatment of lymphatic filariasis due to *Wuchereria bancrofti*.
- Treatment of human sarcoptic scabies.
- Treatment of onchocerciasis due to *Onchocerca volvulus.*
- The safety and efficacy of ivermectin for the treatment of COVID-19 has not been established.

4.2 Posology and method of administration

Posology

Treatment of gastrointestinal strongyloidiasis (anguillulosis)

The recommended dosage is one single oral dose of 200 micrograms of ivermectin per kg body weight.

For guidance, the dose, as determined by the patient's weight, is as follows:

BODY WEIGHT (kg)	DOSE (number of 3 mg tablets)
15 to 24	one
25 to 35	two
36 to 50	three
51 to 65	four
66 to 79	five
≥ 80	six

Treatment of microfilaraemia caused by *Wuchereria bancrofti*

The recommended dosage for mass distribution for the treatment of microfilaraemia caused by *Wuchereria bancrofti* is a single oral dose once every 6 months designed to provide approximately 150 to 200 µg/kg of body weight.

In endemic areas where treatment can only be administered once every 12 months, the recommended dosage is 300 to 400 µg/kg of body weight to maintain adequate suppression of microfilaraemia in treated patients.

For guidance, the dose, as determined by the patient's weight, is as follows:

BODY WEIGHT (kg)	DOSE when given once every 6 months (number of 3 mg tablets)	DOSE when given once every 12 months (number of 3 mg tablets)
15 to 25	one	two
26 to 44	two	four
45 to 64	three	six
65 to 84	four	eight

Alternatively and if no scales are available, the dose of ivermectin for use in mass chemotherapy campaigns may be determined by the patient's height as follows:

HEIGHT (cm)	DOSE when given once every 6 months (number of 3 mg tablets)	DOSE when given once every 12 months (number of 3 mg tablets)
90 to 119	one	two
120 to 140	two	four
141 to 158	three	six
> 158	four	eight

Treatment of human sarcoptic scabies

Treatment is justified when the diagnosis of scabies has been established clinically and/or by parasitological examination. Without formal diagnosis treatment is not justified in case of pruritus.

The recommended dosage is a single oral dose to provide ivermectin 200 µg/kg body weight.

Common scabies:

Recovery will be considered as definite only after 4 weeks of the treatment.

Persistence of pruritus or scraping lesions does not justify a second treatment before this date.

Administration of a second dose within 2 weeks after the initial dose should only be considered:

a) when new specific lesions occur,

b) when the parasitologic examination is positive at this date.

Profuse and crusting scabies:

In these heavily infected forms, a second dose within 8 to 15 days of ivermectin and/or concomitant topical therapy may be necessary to obtain recovery.

Treatment of *Onchocerciasis*

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). The recommended dosage for the treatment of onchocerciasis is a single oral dose designed to provide approximately 150 mcg of ivermectin per kg of body weight. See Table 2 for dosage guidelines. Patients should take tablets on an empty stomach with water. 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.

BODY WEIGHT (kg)	**DOSE (number of 3 mg tablets)**
15 to 25	one
26 to 44	two
45 to 64	three
65 to 84	four
≥ 85	150 mcg/kg

NOTE: ILADEK 3 has no activity against adult *Onchocerca volvulus* parasites. The adult parasites reside in subcutaneous nodules which are infrequently palpable. Surgical excision of these nodules (nodulectomy) may be considered in the management of patients with onchocerciasis, since this procedure will eliminate the microfilariae-producing adult parasites.

Paediatric population

For all indications, safety in paediatric patients weighing less than 15 kg of body weight has not been established.

Method of administration

Oral route.

In children less than 6 years of age, tablets should be crushed before swallowing.

Treatment is one single oral dose taken with water in fasting patient.

The dose may be taken at any time of the day, but no food should be taken within two hours before or after administration, as the influence of food on absorption is unknown.

4.3 Contraindications

Hypersensitivity to the ivermectin or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

Special warnings

Efficacy and dosing regimen of ivermectin in immunocompromised patients being treated for intestinal strongyloidiasis have not been established by adequate clinical studies. There have been reported cases which show the persistence of infestation following a single dose of ivermectin, particularly in this type of patients.

Ivermectin is not a prophylactic therapy of infection with filariae or anguillulosis; there are no data available demonstrating the efficacy of ivermectin, either for killing or preventing the maturation of infective larvae in humans.

Ivermectin has not been shown to have any activity against the adult worm of any species of filariae.

Ivermectin has not been shown to have any beneficial effect on tropical pulmonary eosinophilia syndrome, on lymphadenitis or lymphangitis observed in case of infection with filariae.

The intensity and severity of adverse experiences following administration of ivermectin are probably related to the pretreatment microfilarial density particularly in the blood. In patients co-infected with *Loa loa*, microfilarial density, particularly in the blood, is most often high which predisposes the treated patients to an increased risk in the occurrence of serious adverse experiences. CNS adverse experiences (encephalopathies) have been rarely reported in patients treated with ivermectin and co-infected by a high number of microfilariae of *Loa loa*. Consequently, in *Loa loa* endemic areas, special measures should be taken before any treatment with ivermectin (see section 4.8).

Concomitant treatment with diethylcarbamazine citrate (DEC) and ivermectin in mass chemotherapy campaigns for filariasis caused by *Wuchereria Bancrofti* in Africa is not recommended. Co-infection with other microfilariae, such as *Loa loa* may result in high microfilaraemia in patients infected. Systemic exposure to DEC in such patients may result in the occurrence of serious side effects related to the rapid and effective microfilaricidal effects of this medicine.

Following administration of drugs with a rapid microfilaricidal action such as DEC in patients with onchocerciasis, cutaneous and/or systemic reactions of varying severity (the Mazzotti reaction), and ophthalmological reactions have been reported.

These reactions are probably due to inflammatory responses to degradation products released following the death of microfilariae. Patients treated with ivermectin for onchoceriasis may also experience these reactions when treated for the first time.

After treatment with a microfilaricidal drug, patients with hyperreactive onchodermatitis or “Sowda” (observed particularly in Yemen) may be more likely than others to experience severe cutaneous adverse reactions (oedema and aggravation of onchodermatitis).

Paediatric population

Safety in paediatric patients weighing less than 15 kg of body weight has not been established.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

During mass treatment of onchocerciasis, data on a limited number (approximately 300) of pregnant women indicated no adverse effects such as congenital anomalies, spontaneous abortions, stillbirths and infant mortality which might be associated with ivermectin treatment during the first trimester of pregnancy. To date, no other epidemiological data are available.

Animal studies have shown reproductive toxicity (see section 5.3); however, the predictive value of these observations has not been established.

Breastfeeding

Safety of use has not been established in newborn infants.The treatment to breastfeeding mothers may be only given one week after the birth of the child.

4.7 Effects on ability to drive and use machines

The effect of this medicine on the ability to drive vehicles or operate machinery has not been studied. The possibility of side effects such as dizziness, drowsiness,

vertigo and tremor in some patients that may affect the ability to drive or operate machinery cannot be ruled out (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

Transient hypereosinophilia, liver dysfunction including acute hepatitis, increased liver enzymes, hyperbilirubinaemia and haematuria have been reported.

Very rarely, toxic epidermal necrolysis and Stevens-Johnson syndrome have also been reported.

Side effects are related to the parasite density and are mild and transient in the majority of cases, but their severity may be increased in patients infected with more than one parasite, particularly in the case of infestation with *Loa loa*.

Rarely, severe and potentially fatal cases of encephalopathy have been described following administration of ivermectin, particularly in patients also heavily infected with *Loa loa*. In these patients, the following adverse reactions have also been reported: back or neck pain, ocular hyperaemia, subconjunctival haemorrhage, dyspnoea, urinary and/or faecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor or coma (see section 4.4).

In patients receiving ivermectin for the treatment of strongyloidiasis, the following adverse reactions have been reported: asthenia, abdominal pain, anorexia, constipation, diarrhoea, nausea, vomiting, dizziness, somnolence, vertigo, tremor, transient hypereosinophilia, leukopenia/anaemia and increase in ALAT/alkaline phosphatases.

In the treatment of *Wuchereria bancrofti* filariasis, the intensity of undesirable effects does not seem to be dose-dependent but is related to the microfilarial density in blood. The following have been described: fever, headache, asthenia, feeling of weakness, myalgia, arthralgia, diffuse pain, digestive disorders such as anorexia, nausea, abdominal and epigastric pain, cough, feeling of respiratory

discomfort, sore throat, orthostatic hypotension, chills, vertigo, profuse sweating, testicular pain or feeling of discomfort.

Following administration of ivermectin in patients infected with *Onchocerca volvulus*, the hypersensitivity reactions observed resulting from microfilarial death pertain to Mazzotti-type reactions: pruritus, urticarial rash, conjunctivitis, arthralgia, myalgia (including abdominal myalgia), fever, oedema, lymphadenitis, adenopathies, nausea, vomiting, diarrhoea, orthostatic hypotension, vertigo, tachycardia, asthenia, headache. Rarely, these symptoms have been severe. A few cases of asthma exacerbation have been described. In these patients, abnormal sensation in the eyes, eyelid oedema, anterior uveitis, conjunctivitis, limbitis, keratitis and chorioretinitis or choroiditis have also been described. These manifestations, which may be due to the disease itself, have also been described occasionally after treatment. They were rarely severe and generally resolved without corticosteroid treatment.

Onset of conjunctival haemorrhage has been reported in patients with onchocerciasis.

Observations of adult *Ascaris* expulsion have been described following ingestion of ivermectin.

In patients with scabies, transient exacerbation of pruritus may be observed at the start of treatment.

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Less frequent	Encephalitis
	Frequency	Sore throat, lymphadenitis

MedDRA system organ class	**Frequency**	**Adverse reactions**
	unknown	
Blood and lymphatic system disorders	Frequency unknown	Transient hypereosinophilia, leukopenia/anaemia and increase in ALAT/alkaline phosphatases, adenopathies
Metabolism and nutrition disorders	Less frequent	Anorexia
	Frequency unknown	Asthenia
Psychiatric disorders	Less frequent	Mental status changes, confusion
Nervous system disorders	Less frequent	Lethargy, stupor or coma, drowsiness, dizziness, tremors
	Frequency unknown	Somnolence, vertigo
Eye disorders	Less frequent	Ocular hyperaemia, conjunctival haemorrhage
	Frequency unknown	Conjunctivitis, abnormal sensation in the eyes, eyelid oedema, anterior uveitis, limbitis, keratitis, chorioretinitis or choroiditis
Vascular disorders	Less frequent	Difficulty in standing/walking
	Frequency unknown	Fever, headache, feeling of weakness, orthostatic

MedDRA system organ class	**Frequency**	**Adverse reactions**
		hypotension, chills, profuse sweating, oedema, tachycardia
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea
	Frequency unknown	Cough, feeling of respiratory discomfort, asthma exacerbation
Gastrointestinal disorders	Less frequent	Faecal incontinence
	Frequency unknown	Abdominal and epigastric pain, constipation, diarrhoea, nausea, vomiting
Hepato-biliary disorders	Frequency unknown	Liver dysfunction including acute hepatitis, increased liver enzymes, hyperbilirubinemia and haematuria
Skin and subcutaneous tissue disorders	Less frequent	Toxic epidermal necrolysis and Stevens-Johnson syndrome
	Frequency unknown	Pruritus, urticarial rash
Musculoskeletal and connective tissue disorders	Less frequent	Back or neck pain
	Frequency unknown	Myalgia, arthralgia, diffuse pain
Renal and urinary disorders	Less frequent	Urinary incontinence

MedDRA system organ class	Frequency	Adverse reactions
Reproductive system and breast disorders	Frequency unknown	Testicular pain or feeling of discomfort

c. Description of selected 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 %), diarrhoea (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 %), and urticaria (0.9 %).

In comparative trials, patients treated with ivermectin experienced more abdominal distention 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 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 109 patients given either one or two doses of 170 to 200 mcg/kg ivermectin, the following laboratory abnormalities were seen regardless of

medicine relationship: elevation in ALT and/or AST (2 %), decrease in leukocyte count (3 %). Leukopenia and anaemia were seen in one patient.

Onchocerciasis

In clinical trials involving 963 adult patients treated with 100 to 200 mcg/kg ivermectin, worsening of the following Mazzotti reactions during the first 4 days post-treatment were reported: arthralgia/synovitis (9.3 %), axillary lymph node enlargement and tenderness (11.0 % and 4.4 %, respectively), cervical lymph node enlargement and tenderness (5.3 % and 1.2 %, respectively), inguinal lymph node enlargement and tenderness (12.6 % and 13.9 %, respectively), other lymph node enlargement and tenderness (3.0 % and 1.9 %, respectively), pruritus (27.5 %), skin involvement including oedema, papular and pustular or frank urticarial rash (22.7 %), and fever (22.6 %).

In clinical trials, ophthalmological conditions were examined in 963 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: limbitis: 5.5 %, 4.8 %, and 3.5 % and punctate opacity: 1.8 %, 1.8 %, and 1.4 %. The corresponding percentages for patients treated with placebo were: limbitis: 6.2 %, 9.9 %, and 9.4 % and punctate opacity: 2.0 %, 6.4 %, and 7.2 %.

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 ≥ 1 % of the patients: facial oedema (1.2 %), peripheral oedema (3.2 %), orthostatic hypotension (1.1 %), and tachycardia (3.5 %). Medicine-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 paediatric patients ages 6 to 13.

The following ophthalmological side effects do occur due to the disease itself but have also been reported after treatment with ivermectin: abnormal sensation in the eyes, eyelid oedema, anterior uveitis, conjunctivitis, limbitis, 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 haemoglobin increase (1 %).

Post-Marketing Experience

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

Onchocerciasis

Conjunctival haemorrhage

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**",

found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Cases of accidental overdose with ivermectin have been reported, but none have resulted in fatalities.

In cases of accidental intoxication with unknown doses of products destined for veterinary use (oral use, as an injection, cutaneous use), the symptoms described were: rash, contact dermatitis, oedema, headache, vertigo, asthenia, nausea, vomiting, diarrhoea and abdominal pain. Other effects have also been observed, including: seizures, ataxia, dyspnoea, paraesthesia and urticaria.

Management in case of accidental intoxication:

• symptomatic treatment and surveillance in a medical care setting with fluid replacement and hypertensive treatment, if necessary.

Although there are no specific studies available, it is advisable to avoid combination of GABA agonists in the treatment of accidental intoxication due to ivermectin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 12. Anthelmintics, bilharzia medicines, filaricides, etc.

Pharmacotherapeutic group: Anthelmintics, ATC code: P02CF01

Ivermectin is derived from avermectins isolated from fermentation broths of *Streptomyces avermitilis*. It has high affinity with glutamate-gated chloride channels present in invertebrate nerve and muscle cells. Its binding to these channels promotes an increase in membrane permeability to chloride ions, leading to hyperpolarization of the neural or muscle cell. This results in neuromuscular paralysis and may lead to the death of certain parasites. Ivermectin also interacts

with other ligand-gated chloride channels such as the one involving the GABA neurotransmitter (gamma-aminobutyric acid).

Mammals do not have glutamate-gated chloride channels. Avermectins have only low affinity for other ligand-gated chloride channels. They do not readily cross the blood/brain barrier.

Clinical studies conducted in Africa, Asia, South America, the Caribbean and Polynesia reveal a reduction (to less than 1%) in *Wuchereria bancrofti* microfilaraemia in the week following administration of an oral ivermectin dose of at least 100 µg/kg. These studies showed a dose-dependent effect over the time during which the reduction in microfilaraemia and the infestation rate in the populations treated is maintained.

By treating microfilaraemia in man (the sole parasite reservoir for *Wuchereria bancrofti*), administration of mass treatment seems to be useful in terms of limiting the transmission of *Wuchereria bancrofti* by vector insects and interrupting the epidemiological chain.

Treatment with a single ivermectin dose of 200 micrograms per kg body weight has been shown to be effective and well-tolerated in patients with normal immunity and in whom infestation by *Strongyloides stercoralis* is restricted to the digestive tract.

5.2 Pharmacokinetic properties

Absorption

The mean peak plasma concentration of the major component (H2B1a) observed about 4 hours after oral administration of a single 12 mg dose of ivermectin in tablet form is 46.6 (± 21.9) ng/mL.

Distribution

The plasma concentration increases with increasing doses in a generally

proportional manner.

Biotransformation

Ivermectin is absorbed and metabolized in the human body. An *in vitro* study conducted on human liver microsomes suggests that cytochrome P450 3A4 is the main isoform involved in the hepatic metabolism of ivermectin. In humans, the plasma half-life of ivermectin is about 12 hours and that of the metabolites is about 3 days.

Elimination

Ivermectin and/or its metabolites are excreted almost exclusively in the faeces, whilst less than 1 % of the administered dose is excreted in the urine.

Preclinical studies suggest that ivermectin used at oral therapeutic doses does not significantly inhibit CYP3A4 (IC50 = 50 µM) or other CYP enzymes 2D6, 2C9, IA2 and 2E1.

5.3 Preclinical safety data

Single-dose toxicity studies conducted in animals revealed central nervous system toxicity revealed by the appearance of mydriasis, tremor, and ataxia at high doses in several species (mice, rats and dogs) as well as vomiting and mydriasis in monkeys. After repeated doses of ivermectin close or equal to maternotoxic doses, foetal abnormalities (cleft palate) were observed in several species (mice, rats, rabbits). From these studies, it is difficult to assess the risk associated with the administration of a single low dose. Studies carried out in vitro have not produced any evidence of genotoxicity. However, no genotoxicity or carcinogenicity studies have been performed *in vivo*.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Pregelatinised starch

Butylhydroxyanisole

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ° C

6.5 Nature and contents of container

The tablets are packed in Polyamide/Aluminium/PVC – Aluminium blister.

The blister strips will be packed in cartons with 1, 4,10 or 20 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No specific requirements.

Any unused medication or waste must be disposed of in accordance with the regulations in force.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.

106 16th Road

Midrand

1686

8 REGISTRATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date on the registration certificate of the medicine.

10 DATE OF REVISION OF THE TEXT