

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

STROMEKTOL® ivermectin tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ivermectin 3 mg tablets

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

A white, round, flat tablet with a bevelled edge, engraved with MSD on one side and 32 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Treatment of intestinal strongyloidiasis (anguillulosis).
- Treatment of proven suspected microfilaraemia in patients with lymphatic filariasis caused by *Wuchereria bancrofti*.
- Treatment of human sarcoptic scabies after prior treatment has failed. 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.

4.2 Dose and method of administration

Dose

Treatment of intestinal strongyloidiasis

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

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

Common scabies:

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

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 on an empty stomach.

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. (See section 4.9 and 5.2.)

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 these types 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 or lymphadenitis or lymphangitis observed in case of infection with filariae.

Following administration of ivermectin, the intensity and severity of adverse experiences are probably related to the pre-treatment 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).

Neurological toxicity, including depressed level of consciousness and coma, has also been reported in patients with the use of ivermectin in the absence of *Loa loa* infection. These events have generally resolved with supportive care and the discontinuation of ivermectin. (See Section 4.9.)

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 drug. 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 onchocerciasis may also experience these reactions when treated for the first time. After treatment with a microfilaricidal drug, patients with hyper-reactive 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 Interactions with other medicines and other forms of interaction

Very rarely, post-marketing reports of increased INR (International Normalised Ratio) have been reported when ivermectin was co-administered with warfarin.

4.6 Fertility, pregnancy and lactation

Pregnancy

STROMEKTOL should not be used in pregnancy as safety in pregnancy has not been established.

Data on a limited number (approximately 300) of exposed pregnancies in mass treatment campaigns for onchocerciasis, indicate no adverse effects, like congenital anomalies, spontaneous abortions, foetal deaths/stillbirths and infant mortalities, after ivermectin use in the first trimester. To date, no other epidemiological data are available.

Animal studies have shown reproductive toxicity (see section 5.3); however, the potential risk for humans is unknown.

Ivermectin should only be used when strictly indicated.

Lactation

Less than 2% of the administered dose of ivermectin appeared in breast milk.

Safety in newborn infants has not been established; therefore, the drug should be given to nursing mothers only if the benefit to the mother outweighs the potential risk to the breast-fed infant, and treatment of mothers who intend to breast feed their infants should be delayed until 1 week after birth of the child.

4.7 Effects on ability to drive and use machines

It is not known if ivermectin has an influence on the ability to drive and use machines. Possible side effects such as dizziness, somnolence, vertigo and tremor may affect

some patients' ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Side effects are related to the microfilarial density and most of them are mild and transient in nature but the incidence and severity may be higher in patients infected with more than one parasite, as in the case of infection with *Loa loa*.

Rarely, patients who are also heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy following treatment with ivermectin. In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival haemorrhage, dyspnoea, urinary and/or faecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma (see section 4.4).

In the treatment of strongyloidiasis, the following side effects have been reported after ivermectin therapy: asthenia, abdominal pain, anorexia, constipation, diarrhoea, nausea, vomiting, dizziness, somnolence, vertigo, tremor, transient eosinophilia, leukopaenia/anaemia and increase in ALT/alkaline phosphatases.

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.

Following treatment of patients infected with *Onchocerca volvulus* with ivermectin, the following hypersensitivity reactions may occur due to the death of microfilariae: these are symptoms of Mazzotti type reactions: pruritus, frank urticarial rash, conjunctivitis, arthralgia, myalgia (including abdominal myalgia), fever, oedema, lymphadenitis, lymphadenopathies, nausea, vomiting, diarrhoea, orthostatic hypotension, vertigo, tachycardia, asthenia, headache. These reactions have been rarely severe. Some cases of worsening of bronchial asthma have been reported.

In these patients, abnormal sensation in eyes, eyelid oedema, anterior uveitis, conjunctivitis, limbitis, keratitis and chorioretinitis or chorioiditis, have also been described. These reactions can occur due to the disease itself, but have occasionally been reported after therapy. These have rarely been severe and have generally resolved without corticosteroid treatment.

Transient hypereosinophilia, liver function abnormalities and haematuria have been reported.

Cases of ascaris expulsion of adult worms have been described following administration of ivermectin.

In patients with scabies, transient exacerbation of pruritus may be noted at the beginning of treatment.

Post Marketing Experience

Onchocerciasis

Conjunctival haemorrhage

All indications

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

Neurological toxicity including depressed level of consciousness and coma (see section 4.4).

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

It is important to adhere to recommended dosages. Cases of depressed levels of consciousness and coma have been reported with overdosage of ivermectin.

In accidental intoxication with unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, injection, exposure to body surfaces, the following symptoms have been reported: rash, contact dermatitis, oedema, headache, vertigo, asthenia, nausea, vomiting, diarrhoea and abdominal pain. Other adverse effects that have been reported include: seizures, ataxia, dyspnoea, paresthesia, and urticaria.

Management in case of accidental poisoning:

- symptomatic treatment and supervision in specialised care unit with fluid replacement and hypertensive treatment if necessary. Although there are no data available, it seems advisable to avoid the use of GABA agonists in the treatment of accidental intoxications due to ivermectin.

In a study in which healthy volunteers were orally administered up to 2000 mcg/kg ivermectin in a fasted state or up to 600 mcg/kg ivermectin following a high-fat (48.6 g of fat) meal, there were no indications of central nervous system toxicity observed at any dose irrespective of food intake. (see section 5.2.)

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: P02CF01

Anthelmintic.

Ivermectin is derived from the avermectins, that are isolated from fermentation of *Streptomyces avermitilis*. It binds 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 hyperpolarisation of the nerve or muscle cell, resulting in paralysis and death of the parasite.

Ivermectin interacts also with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

Mammals do not have glutamate-gated chloride channels. The avermectins have a low affinity for mammalian ligand-gated chloride channels. They do not readily cross the blood-brain barrier in humans.

Clinical studies in patients with microfilaraemia caused by *Wuchereria bancrofti* conducted in Africa, Asia, South America, the Caribbean and Polynesia demonstrated that a single oral dose of at least 100 µg/kg ivermectin resulted in reduction of microfilaraemia to below 1% of the pre-treatment value in the week following administration. These studies showed that the treatment effect was dose-dependent in both the extent and the duration.

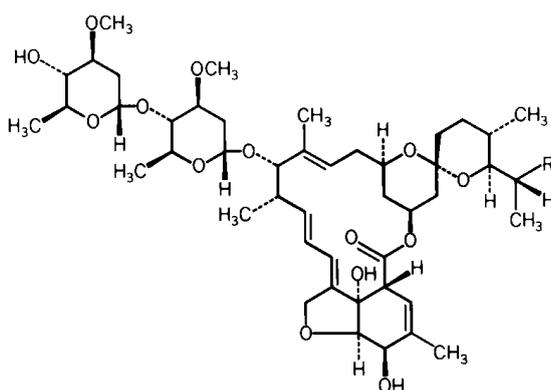
The use of ivermectin in mass treatment of populations for the treatment of microfilaraemia in man, the unique host for *Wuchereria bancrofti*, may be useful to decrease the transmission of *Wuchereria bancrofti* by vector insects, thus interrupting the infectious cycle of the disease.

Treatment with a single dose of 200 µg/kg ivermectin has been shown to be effective and well-tolerated in patients with a normal immunity and for whom infestation by *Strongyloides stercoralis* is limited to the digestive tract.

Chemistry

Ivermectin tablets contain a mixture of at least 90% 22,23-dihydroavermectin B_{1a} and 10% or less of 22,23-dihydroavermectin B_{1b}.

The structural and empirical molecular formulas are indicated below.



Component B_{1a}, R = C₂H₅

Component B_{1b}, R = CH₃.

Molecular Formula: H₂B_{1a} C₄₈H₇₄O₁₄ (R = C₂H₅)
 H₂B_{1b} C₄₇H₇₂O₁₄ (R = CH₃)

Molecular Weight: H₂B_{1a} 875.10 (R = C₂H₅)
 H₂B_{1b} 861.07 (R = CH₃)

Bulk ivermectin contains a minimum of 90% of the compound wherein the R group (see structure) is ethyl and 10% or less of the compound in which R is methyl.

Ivermectin is a white to yellowish-white, nonhygroscopic, crystalline powder which is practically insoluble in water, freely soluble in methanol and soluble in 95% ethanol.

5.2 Pharmacokinetic properties

With 12 mg single oral doses of STROMEKTOL administered as tablets, the mean peak plasma concentration of the major component (H2B_{1a}) was 46.6 (\pm 21.9) ng/mL at approximately 4 hours after dosing.

Plasma concentration increases with increasing dose in a manner approximately proportional to the dose. Ivermectin is metabolised in humans, and ivermectin and/or its metabolites are excreted almost exclusively in the faeces over an estimated 12 hours with less than 1% of the administered dose being excreted in the urine. The plasma half-life of ivermectin in man is about 12 hours and that of the metabolites is about 3 days.

In vitro studies have shown that ivermectin is primarily metabolised by CYP3A4. Preclinical studies suggest that ivermectin has limited potential to inhibit CYP3A4 at clinical doses and no potential to inhibit other CYP enzymes (2D6, 2C9, 1A2, and 2E1).

A multiple-dose (30 to 120 mg [333 to 2000 mcg/kg]) clinical safety study has been conducted to assess the safety and pharmacokinetic properties of ivermectin in 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. However, there were no indications of central nervous system toxicity associated with either regimen. (See section 4.9.)

5.3 Preclinical safety data

Single dose toxicity studies revealed central nervous toxicity evidenced by mydriasis, tremors, and ataxia at high doses in several animal species (mice, rats, and dogs) and emesis and mydriasis (monkeys). After administration of repeated doses of ivermectin close to or equal to maternotoxic doses, foetal abnormalities (cleft palates) have been observed in several animal species (mice, rats, rabbits). From these studies, it is difficult to assess the risk of a single low dose. *In vitro* ivermectin was not genotoxic, however *in vivo* genotoxicity and carcinogenicity data are lacking.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, pregelatinised corn starch, butylated hydroxyanisole, citric acid, magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

The tablets are packaged in aluminium foil blister packs in cardboard cartons. Pack size: 4 and 20* tablets.

* Pack size not available.

6.6 Special precautions for disposal

No special requirements.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Merck Sharp & Dohme (NZ) Ltd
P O Box 99851
Newmarket
Auckland
NEW ZEALAND
Tel: 0800 500 673

9 DATE OF FIRST APPROVAL

18 August 2005

10 DATE OF REVISION OF THE TEXT

16 August 2023

SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|-----------------|-----------------------------|
| | Copyright statement revised |

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