PRODUCT INFORMATION

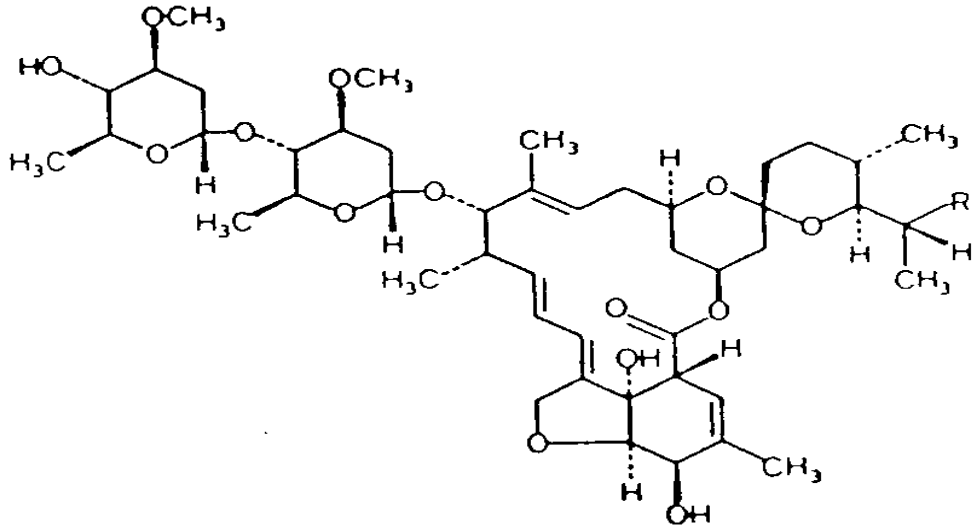
STROMECTOL® TABLETS
(ivermectin 3 mg)

NAME OF THE MEDICINE
STROMECTOL® (ivermectin) 3 mg tablet

DESCRIPTION
Ivermectin is derived from the avermectins, a class of highly active broad-spectrum antiparasitic agents isolated from fermentation broths of *Streptomyces avermitilis*.

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

The structural and molecular formulae follow.



Molecular Formulae:	Molecular Weight:		
22, 23-dihydroavermectin B_{1a}	$C_{48}H_{74}O_{14}$	(R=C_2H_5)	875.10
22, 23-dihydroavermectin B_{1b}	$C_{47}H_{72}O_{14}$	(R=CH_3)	861.07

Ivermectin contains a minimum of 90% of 22, 23-dihydroavermectin B_{1a} (where the R group is ethyl) and a maximum of 10% of 22, 23-dihydroavermectin B_{1b} (the R group is methyl).

STROMECTOL is supplied as a 3 mg tablet. STROMECTOL tablets also contain microcrystalline cellulose, pregelatinised maize starch, magnesium stearate, butylated hydroxyanisole and citric acid anhydrous.

PHARMACOLOGY

Ivermectin inhibits signal transmission from the ventral cord interneurons to the excitatory motor neurones in nematodes by stimulating release of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) from pre-synaptic nerve terminals. In arthropods, a similar mechanism inhibits signal transmission at the neuromuscular junction. Ivermectin does not readily penetrate the CNS of mammals, and thus does not interfere with mammalian GABA-dependent neurotransmission.

Pharmacokinetics:

Absorption and Distribution:

Ivermectin is incompletely absorbed (~50% bioavailable relative to an oral hydroalcoholic solution) following oral doses of ivermectin tablets, with a Tmax of ~4 hours. With 12 mg single dose tablets administered in healthy male volunteers, the mean peak plasma concentration of the major component was 46.6 (± 21.9) ng/mL (range 16.4-101.1 ng/mL).

Administration of 30 mg (333 to 600 µg/kg) 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 healthy volunteers.

Metabolism and Excretion:

Ivermectin is metabolised in humans, and ivermectin and/or its metabolites are excreted almost exclusively in the faeces over an estimated 12 days 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 (9.8-14.3 h) and that of the metabolites is about 3 days.

The pharmacokinetics of ivermectin has not been studied in patients with impaired hepatic or renal function.

CLINICAL TRIALS

Onchocerciasis in Adults:

A total of 758 adult patients with onchocerciasis received a single oral dose of 150-220 µg/kg ivermectin in three studies. In these studies, a significant reduction in microfilarial counts was reported in evaluable patients who received ivermectin, compared to those who received diethylcarbamazine or placebo. At 2-4 days after ivermectin dosing, microfilariae (mf) counts less than 5 per mg skin were reported in 29% to 96% of evaluable subjects, at 3 months after dosing < 5 mf/mg were reported in 88% to 96% of evaluable subjects, and at 12 months after dosing < 5 mf/mg were reported in 48% to 62% of evaluable patients. In patients with ocular involvement there was a significant reduction in intraocular microfilariae maintained for up to 12 months.

Onchocerciasis in Children:

In an open study, ivermectin reduced skin microfilaria in children with onchocerciasis for up to 12 months. One hundred and three (103) children aged between 5 to 12 years were treated with the targeted dose of 150 μm/kg ivermectin as a single oral dose. Resulting geometric mean microfilariae (mf) counts fell from a pre-treatment value of 36.4 mf/mg skin to 5.8%, 0.7%, 2.2% and 5.4% of the pre-treatment value on day 3, month 3, month 6 and month 12 respectively.

Intestinal Strongyloidiasis:

Two controlled clinical studies using albendazole as the comparative agent were carried out in countries where albendazole is approved for the treatment of strongyloidiasis of the gastrointestinal tract, and two controlled studies were carried out using thiabendazole as the comparative agent. Efficacy, as measured by cure rate, was defined as the absence of larvae in follow-up stool examinations post-therapy. Based on this criterion, efficacy was significantly greater for ivermectin (a single dose of 170 to 200 μg/kg) than for albendazole (200 mg b.i.d. for 3 days). Ivermectin administered as a single dose of 200 μg/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 Comparative Agents in the Treatment of Strongyloidiasis

	Cure Rate* (%)	
	Ivermectin**	Comparative Agent
Albendazole***		
Comparative		
International Study	22/28 (79)	10/23 (43)
WHO Study	126/152 (83)	67/149 (45)
Thiabendazole†		
Comparative		
International Study	10/15 (67)	13/15 (87)
US Study	14/14 (100)	16/17 (94)

* Number and % of evaluable patients
** 170-200 μg/kg
*** 200 mg b.i.d. for 3 days
† 25 mg/kg b.i.d. for 3 days

Sarcoptes Scabiei:

Classic variety/Typical Scabies:

The clinical data evaluated for this indication were from a literature-based submission which uncovered 8 randomized controlled trials of ivermectin in typical scabies (see References), as well as a number of reviews, including a 2010 Cochrane Review (Strong and Johnstone, 2010).

Placebo-controlled studies
Macotela-Ruiz *et al*. (1993) conducted a trial comparing a single dose of ivermectin 200 µg/kg body weight with placebo in the treatment of scabies in 55 patients. The authors found that 26 (79.3%) patients were cured, defined as absence of itching and no dermatologically active lesions, with ivermectin on their first follow-up visit vs. 4 (16%) in the placebo group ($p<0.001$). The overall cure rates were 37 (74%) and 4 (16%) for ivermectin and placebo, respectively ($p<0.001$).

Active-comparator trials
Bachewar *et al*. (2009) conducted a non-blinded, prospective, randomized trial comparing benzyl benzoate 25% lotion (applied nightly for 2 nights), permethrin 5% cream (applied once), and a single dose of ivermectin 200 µg/kg body weight in 103 patients with noncrusted scabies. The primary outcome of interest was cure rate, defined as no lesions, measured after 1 and 2 weeks.

After 1 week, the cure rates were 76%, 82.1%, and 55.6% for benzyl benzoate, permethrin, and ivermectin, respectively ($p<0.05$ for permethrin vs. ivermectin). After 2 weeks, the cure rates were 92% for benzyl benzoate, 96.4% for permethrin, and 100% for ivermectin.

Chouela *et al*. (1999) compared ivermectin and lindane in a randomized, controlled, double-blind study in 53 patients with scabies. Patients received either a single oral dose of ivermectin 150-200 µg/kg body weight or topical application of 1% lindane solution. Treatment was repeated if clinical cure had not occurred, with clinical cure defined as absence of both pruritus and clinical lesions or a reduction in severity of signs and symptoms to ‘mild’.

At day 15, 14/19 (74%) patients in the ivermectin group showed healing compared with 13/24 (54%) in the lindane group ($p=0.22$). At day 29, 18/19 (95%) patients receiving ivermectin were healed, and 23/24 (96%) receiving lindane were healed ($p>0.99$).Further analysis of the equivalence of therapeutic efficacy showed that ivermectin was statistically no less efficacious than lindane ($p<0.02$).

Ly *et al*. (2009) compared 2 regimens of benzyl benzoate (BB) and ivermectin in a randomized, open-label trial in 181 patients with scabies. BB was administered as either one application of 12.5% benzyl benzoate which was not removed for 24 hours (BB1), or as two such applications, each over 24 hours (BB2). Ivermectin was administered as a single oral dose of 150-200 µg/kg body weight.

The primary outcome measure was complete disappearance of visible lesions and itching at day 14. Patients who had clearly worsened at day 7 were given the same treatment as the week before. If no change was noted at day 7 or if the patient had improved, nothing further was done until day 14. If treatment failure was observed at day 14, the treatment was applied again. If treatment failure was observed again at day 28, patients in the BB1 and ivermectin groups were switched to the BB2 application, and those in the BB2 group were switched to ivermectin.

For the primary endpoint of efficacy at day 14, cure rates were 37/68 (54.4%) with BB1, 33/48 (68.8%) with BB2, and 16/65 (24.6%) with ivermectin, with a significance level of $p<10^{-6}$ overall. The comparison of BB1 and BB2 combined was also superior to ivermectin ($p<10^{-5}$). At day 28, cure rates were 52/68 (76.5%) for BB1, 46/48 (95.8%) for BB2, and 28/65 (43.1%) for ivermectin ($p<10^{-5}$ overall).

Madan *et al*. (2001) compared ivermectin and 1% topical lindane solution in a randomized trial in 200 patients with scabies. Patients received either a single dose of ivermectin 200 µg/kg body weight or 1% lindane topical solution applied overnight for 1 night. Efficacy was evaluated over the first 3 days, and at 2 weeks and 4 weeks. Improvement was measured on a categorical scale of: Complete/100% (no signs or symptoms of scabies); Good/75% (itching absent, lesions except burrows present; Moderate/50% (Itching markedly reduced, burrows +); Slight/25% (Itching slightly reduced, burrows ++); Poor/0% (no improvement); Negative (Further aggravation/exacerbation).

After 48 hours of treatment, no patients in either treatment group reported complete improvement, but 17.5% of patients in the ivermectin group and 7.1% in the lindane group reported good improvement. After 2 weeks, 36.1% of patients in the ivermectin group had complete improvement compared with 22.4% in the lindane group. At 4 weeks, 82.6% of patients in the ivermectin group had complete improvement compared with 44.4% in the lindane group. After 4 weeks, 2.8% of patients in the ivermectin group reported negative improvement compared with 4.9% in the lindane group.

Mushtaq *et al*. (2010) compared ivermectin and permethrin 5% cream in 100 patients with scabies. Patients received either a single dose of ivermectin 200 µg/kg body weight or a single application of topical permethrin 5% cream at night on the whole body for 12 hours. Patients not responding after the 1 week dose were given a second dose. Efficacy was determined by disappearance of itching, clearance of skin lesions, and absence of mites on microscopy of skin lesions.

Two weeks after the first dose, 24 (54.5%) patients in the ivermectin group were cured of disease, and 20 (47.6%) were cured in the permethrin group (p=0.5). Cure rates at 4 weeks were 79.5% and 88.1%, respectively (p=0.157). Itching at 4 weeks was mild in 6.8% of patients in the ivermectin group, and 2.4% in the permethrin group. No patients in either group had positive mite scrapings at week 2.

Nnoruka and Ague (2001) evaluated ivermectin and 25% benzyl benzoate topical application in an uncontrolled prospective study in 58 patients with scabies. Patients received ivermectin as a single oral dose at 200 µg/kg body weight or 25% benzyl benzoate applied from neck to toes for 72 hours. Clinical scores were calculated using skin lesions located in 16 different locations of the body. An area was given a score of 2 if there was at least one active lesion, a score of 1 if the most important lesion was healed, and a score of 0 if there was no lesion present. A classical burrow was scored a 2. A patient's clinical score was the sum off all individual area scores, which could range from 2 to 30 at study entry and from 0 to 30 at subsequent visits. In addition, pruritus was measured on a 10 cm visual analogue scale, where 0 = not present and 10 = extremely severe.

Mean clinical scores at baseline were 16.1 for ivermectin and 16 for benzyl benzoate. At day 7, scores were 5.4 and 10.3, respectively. At day 14 scores were 2.3 and 6.1, respectively, and at day 30 scores were 1.1 and 3.5 respectively. Analysis of variance showed a significant decrease in scores with ivermectin (p=0.004). At day 7, 31% of patients receiving ivermectin had complete disappearance of lesions and pruritus. On day 14, 65.3% of patients receiving ivermectin and 34.5% of patients receiving benzyl benzoate were healed. By day 30, 93.7% of patients receiving ivermectin were healed. By day 30, response to pruritus was rated as excellent in 93.1% of patients receiving ivermectin, and 48.3% in patients receiving benzyl benzoate.

Usha and Nair (2000) conducted a randomized trial comparing ivermectin and permethrin cream in the treatment of scabies in 85 patients and their family contacts. Ivermectin was administered as a single oral dose of 200 µg/kg body weight, and 5% permethrin cream was given as a single overnight topical application. Treatment was considered to be effective if, after 2 weeks, there was improvement in pruritus (measured on a visual analogue scale), clinical improvement in skin lesions with no new lesions, and absence of mites or the products on microscopy. Improvement was considered mild if there was less than 50% reduction in the number of lesions and pruritus; moderate if there was more than 50% reduction; and good if there was complete clearance. Treatment was considered a failure if, after 2 weeks, there was no improvement in pruritus and skin lesions, appearance of new lesions, or presence of mites or their products on microscopy. In the case of treatment failure, another dose of the randomized treatment was repeated. If the repeat treatment failed, patients were crossed over to the other treatment group. The primary endpoint was the complete disappearance of clinical signs and symptoms and no appearance of new lesions at the end of 2 months after the last dose was taken.

After the first week, 50% of patients in the ivermectin group and 84.3% of patients in the permethrin group had symptom improvement. By the second week, 70% in the ivermectin group and 97.8%, in the permethrin group improved. By the fourth week, 95% of patients in the ivermectin and 100% of patients in the permethrin groups improved. Two (5%) patients did not respond to 2 doses of ivermectin; both were cured after crossing over to permethrin after a single application. There was no recurrence of scabies at the end of 2 months of follow-up in either group. Complete clearance of lesions (graded as “good” improvement) occurred earlier with permethrin than with ivermectin, with significant differences at weeks 1 ($p=0.03$), 2 ($p=0.003$), and 4 ($p=0.0005$). At 8 weeks, all patients were completely cured ($p=0.21$).

Crusted variety:

No randomised controlled trials in crusted scabies have been reported in the literature. A systematic review of the literature on crusted scabies identified observational studies, case series and individual case reports in which 260 patients (mean age (range) 41.7 years (2-94 years)) received ivermectin. Of these cases, 182 received ivermectin at a dose of 200 µg/kg of body weight.

Seventy eight percent (78%) of all patients were managed in a clinic setting following confirmation of high mite count. The majority of patients for whom this was reported (70%) received ivermectin after proving refractory to classical topical treatments.

At least 72% of cases were treated with combination ivermectin and topical scabicide. In the large Australian cohort studies, all patients were administered topical keratolytic therapy in keeping with Australian clinical protocols.

Ivermectin was shown to have an overall clinical efficacy across these publications of an 87% cure rate, however, this must be interpreted with caution because of the potential for publication bias (i.e. publication of cases with good outcomes). The majority of patients presenting with mild to severe forms of crusted scabies were adequately managed with one to two oral doses of 200 µg/kg ivermectin. One to two doses may not be adequate in treating very severe cases of crusted scabies.

INDICATIONS
STROMECTOL (ivermectin) is indicated for the treatment of:
a) onchocerciasis and intestinal strongyloidiasis (anguillulosis).
b) crusted scabies in conjunction with topical therapy.
c) human sarcoptic scabies when prior topical treatment has failed or is contraindicated.

Treatment is only 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 alone.

CONTRAINDICATIONS
Hypersensitivity to any component of the product.

PRECAUTIONS
If any hypersensitivity reaction to this product occurs, no further dose should be given.

Effects on fertility:

No data are available.

For treatment of onchocerciasis:

Ivermectin should be used only when infections with *O. volvulus* have been diagnosed or are suspected. No data are available to support its use prophylactically.

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

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 haemorrhage, dyspnoea, urinary and/or faecal 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.

Impaired Renal or Hepatic function:

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

Use in Pregnancy (Category B3):

Ivermectin should not be used in pregnancy as safety in pregnancy has not been established. Ivermectin caused cleft palates in mice and rats at oral doses of 0.4 and 10 mg/kg/day respectively, and cleft palates and clubbed feet in rabbits dosed at 3 mg/kg/day.

Use in Lactation:

Ivermectin is excreted in breast milk and safety in newborn infants has not been established. In rats, reduced survival occurred in control pups and pups exposed in utero that were cross-fostered to treated dams, but not in control pups or pups exposed in utero cross-fostered to control dams.

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 the treatment of mothers who intend to breast-feed their infants should be delayed until at least one week after the birth of the child.

Carcinogenicity/Mutagenicity:

There have been no carcinogenicity studies with ivermectin. Ninety-four and 105 week carcinogenicity studies on mice and rats respectively were conducted with the closely related compound abamectin and were negative at up to 8 mg/kg/day in mice and up to 2 mg/kg/day in rats. Ivermectin was negative in three *in vitro* assays for geno toxicity (mutagen assays in bacteria and mouse cells, and unscheduled DNA synthesis in human cells). No tests have been done to test the potential of ivermectin for producing clastogenicity.

Paediatric Use:

Onchocerciasis:

Ivermectin should not be used in children under five years of age as safety in this age group has not been established.

The safety profile of ivermectin in children 5 to 12 years of age is similar to that observed in adults (see ADVERSE EFFECTS/Onchocerciasis).

Strongyloidiasis:

Efficacy has not been established in children under twelve years of age.

***Sarcoptes scabiei* (scabies):**

Ivermectin should not be used in children under 15 kg and under 5 years of age as safety in these groups has not been established.

Use in the Elderly:

Clinical studies of STROMECTOL did not include sufficient numbers of elderly subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, treatment of elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Effects on laboratory tests:

No data are available.

INTERACTIONS WITH OTHER MEDICINES

Interactions between ivermectin and other drugs have not been studied in clinical trials.

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

ADVERSE EFFECTS
A. CLINICAL TRIAL AND PUBLISHED DATA

A.1. Strongyloidiasis:

Ivermectin has been demonstrated to be generally well tolerated in the treatment of strongyloidiasis.

In three clinical studies involving a total of 109 patients given either one or two doses of 170-200 μg/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%)

Ivermectin was better tolerated than thiabendazole in comparative studies involving 37 patients treated with thiabendazole.

In a WHO sponsored study, children and adults (9-22 years) with strongyloidiasis were treated with ivermectin 200 μg/kg as a single dose or albendazole 200 mg twice daily for 3 days. The safety results are summarised in the following table:

WHO Study - Number of Patients Developing Adverse Effects Within 3 Days After Treatment, Regardless of Drug Relationship

Body System/ Symptoms	Ivermectin (n=163)	Albendazole (n=170)
Body As A Whole		
Abdominal Distension	7*	1
Chest Pain/Tightness	7*	0
Fever	10	7
Digestive System		
Loose Stools	16	17
Nausea	5	6
Watery Diarrhoea	2	3
Nervous System		
Headache	15	18
Dizziness, vertigo	5	10
Skin		
Diffuse Itching	3	6
Respiratory System		
Cough	11	8

* = $p < 0.05$

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 EFFECTS, Onchocerciasis).

Laboratory Test Findings:

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

A.2. Onchocerciasis:

Ivermectin has been demonstrated to be generally well tolerated in the treatment of onchocerciasis.

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-type 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.

In clinical trials involving 963 adult patients treated with 100 to 200 μg/kg ivermectin and 315 patients on placebo, worsening of the following Mazzotti-type reactions during the first 4 days post-treatment were reported (ivermectin, placebo, respectively): arthralgia/synovitis (9.3%, 4.4%), axillary lymph node enlargement (11.0%, 2.9%), axillary lymph node tenderness (4.4%, 1.0%), cervical lymph node enlargement (5.3%, 4.1%), cervical lymph node tenderness (1.2%, 0.6%), inguinal lymph node enlargement (12.6%, 6.7%), inguinal lymph node tenderness (13.9%, 5.7%), other lymph node enlargement (3.0%, 1.6%), other lymph node tenderness (1.9%, 0.6%), pruritus (27.5%, 17.2%), skin involvement including oedema, papular and pustular or frank urticarial rash (22.7%, 9.2%), and fever (22.6%, 4.8%).

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 μg/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 μg/kg ivermectin and 315 patients on placebo, the following clinical adverse reactions were reported as possibly, probably, or definitely related to the drug in ≥ 1% of the patients (ivermectin and placebo, respectively): facial oedema (1.2%, 0%), peripheral oedema (3.2%, 0.6%), orthostatic hypotension (1.1%, 0%), and tachycardia (3.5%, 0.6%). Drug-related headache and myalgia occurred in < 1% of patients given ivermectin (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 5 to 12.

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 (ivermectin and placebo, respectively): oeosinophilia (3%, 0%) and haemoglobin increase (1%, 0%).

A.3. *Sarcoptes scabiei* (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 sensitisation of the human host to mite antigens, with a consequent immunologic reaction (1.4%). Sensitisation 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.

B. 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, elevation of liver enzymes and elevation of bilirubin.

DOSAGE AND ADMINISTRATION
STROMECTOL is available as white tablets each containing 3 mg ivermectin. Treatment is administered as a single oral dose given with water.

The dose is determined by the patient's weight as shown below.

Strongyloidiasis - the dosage aims to provide approximately 200 µg ivermectin/kg body weight.

Dosage in Strongyloidiasis:	
Body Weight (Kg):	Dose (Number of 3 mg tablets):
15-24	One
25-35	Two
36-50	Three
51-65	Four
66-79	Five
≥ 80	Approx 200 µg/kg
In general, additional doses are not necessary, however, a follow-up examination of stool to verify efficacy should be performed.	

Onchocerciasis - the dosage aims to provide approximately 150 µg ivermectin/kg body weight.

Dosage in Onchocerciasis:	
Body Weight (Kg):	Dose (Number of 3 mg tablets):
15-25	One
26-44	Two
45-64	Three
65-84	Four
Alternatively, the dose of ivermectin for use in mass chemotherapy campaigns may be determined by the patients height, as follows:	
Height (cm):	Dose (Number of 3 mg tablets):
90-119	One
120-140	Two
141-158	Three
> 158	Four
[Reference: Alexander, N.D.E., ivermectin dose assessment without weighing scales. Bulletin of the World Health Organisation, 71 (3/4): 361-366 (1993)]	
The suggested dose interval for most patients is 12 months. At some sites it may be preferable to use a 6 months interval depending on such considerations as density of skin microfilariae and/or prevalence.	

***Sarcoptes scabiei* (scabies)** - the dosage aims to provide approximately 200 µg ivermectin/kg body weight per dose.

Dosage in Sarcoptes scabiei (scabies)	
Body Weight (Kg):	Dose (Number of 3 mg tablets):
15-24	One
25-35	Two
36-50	Three
51-65	Four
66-79	Five
> 80	Approx 200 µg/kg

Classic/typical scabies: 2 doses (1 dose on day 1 and another dose between day 8 and day 15). Ivermectin can be used alone or in combination with a topical scabicide.

Crusted scabies (ivermectin in combination with a topical scabicide administered as):

- Mild cases: 2 doses (1 dose on day 1 and another dose between day 8 and day 15)
- Moderate to severe cases: More than 3 doses may be required for effective treatment.

Patients with crusted scabies should use keratolytics on days they are not treated with topical scabicides to assist with the reduction of scaling that harbours the mite. Consultation with a dermatologist or infectious diseases physician is recommended.

The life cycle of *S. scabiei* begins with the pregnant female laying two to three eggs a day in burrows several millimetres to several centimetres in length in the stratum corneum (outermost layer) of the skin. The eggs hatch in two weeks. The larvae form intra-epidermal lesions whilst they mature into the adult form. This maturation takes 2-3 weeks.

OVERDOSAGE

There are reports of accidental overdosing of ivermectin, but no fatalities have been attributable to ivermectin overdosing.

In significant accidental intoxication with unknown quantities of a veterinary formulation, symptoms have resembled those seen in animal toxicology studies, which were chiefly rash, contact dermatitis, oedema, headache, dizziness, asthenia, nausea, vomiting, diarrhoea, mydriasis, somnolence, depressed motor activity, tremors and ataxia. Other adverse effects that have been reported include: seizure, dyspnoea, abdominal pain, paraesthesia and urticaria.

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 antipoison measures may be indicated if needed to prevent absorption of ingested material. Although data are not available for man, it would appear advisable to avoid GABA-agonistic drugs in the treatment of accidental ivermectin intoxication.

In a study in which healthy volunteers were orally administered up to 2000 µg/kg ivermectin in a fasted state or up to 600 µg/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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Presentation:

STROMECTOL is available as white, round, flat tablets with a bevelled edge, engraved with MSD on one side and 32 on the other side and containing 3 mg ivermectin. The tablets are packaged in aluminium foil blister packs in cardboard cartons. Pack size: 4 tablets.

Storage Instructions:

Store below 30°C.

NAME & ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty Ltd
Level 1, Building A
26 Talavera Road
Macquarie Park NSW 2113
Australia

POISION SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):
Approved by the Therapeutic Goods Administration: 27th August 1999.

Date of most recent amendment:
31 October 2014

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