SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ivermectin 3 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 3 mg of ivermectin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Round, white tablets with no marks of approximately 5mm.of diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of intestinal strongyloidiasis (anguillulosis).
- Treatment of proven or suspected microfilaremia in patients with lymphatic filariasis caused by *Wuchereria bancrofti*.
- 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.

Official guidelines should be taken into consideration. Official guidelines will normally include WHO and public health authorities' guidelines.

8.2 Posology and method of administration

Posology

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 microfilaremia caused by Wuchereria bancrofti

The recommended dosage for mass distribution for the treatment of microfilaremia 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 microfilaremia 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 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 pediatric 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.

4.3 Contraindications

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

12.4 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.

Following administration of ivermectin, the intensity and severity of adverse experiences 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).

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 i*nfection. These events have generally resolved with supportive care and the discontinuation of ivermectin. (See sections 4.8 and 4.9).

Concomitant treatment with 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 diethylcarbamazine citrate (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 hyperreactive onchodermatitis or "Sowda" (observed particularly in Yemen) may be more likely than others to experience severe cutaneous adverse reactions (edema and aggravation of onchodermatitis).

Severe cutaneous adverse reactions (SCARs)
Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported with ivermectin treatment (see section 4.8).
At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, ivermectin should be withdrawn immediately and an alternative treatment considered. If the patient has developed a severe cutaneous adverse reaction such as SJS or TEN with the use of ivermectin, treatment with ivermectin must not be restarted at any time.

In the absence of convincing evidence of efficacy (and safety) for use of ivermectin as a treatment for COVID-19 it is strongly recommended that ivermectin is not used for the treatment of patients with or suspected to be infected with SARS-COV2 as this may lead to a delay in diagnosis and /or receiving appropriate treatment for COVID-19. The extent and risks of such use will be monitored as part of the risk management plan.

Precautions for use

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

4.5 Interaction with other medicinal products and other forms of interaction

No interactions studies have been performed.

16.6 Fertility, pregnancy and lactation

Pregnancy

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, fetal 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.

Breastfeeding

Less than 2% of the administered dose of ivermectin appears 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.

20.7 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).

24.8 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 serious or even fatal encephalopathy following treatment with ivermectin.

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.

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, edema, lymphadenitis, lymphadenopathies, nausea, vomiting, diarrhea, 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 the eyes, eyelid edema, anterior uveitis, conjunctivitis, limbitis, keratitis and chorioretinitis or choroiditis, have also been described. These reactions can occur due to the disease itself, but have also occasionally been reported after theraphy. These have rarely been severe and have generally resolved without corticosteroid treatment.

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.

Tabulated list of adverse reactions

Table 1: Adverse Reactions with Ivermectin

MedDRA System Organ Class	**Frequency**	**Adverse Reaction(s)**
Blood and lymphatic system disorders	Not known	Transient eosinophilia, leukopaenia/anaemia[1]
Metabolism and nutrition disorders	Not known	Anorexia[1, 2]
Psychiatric disorders	Not known	Mental status changes[3]
Nervous system disorders	Not known	Encephalopathy[3], depressed level of consciousness, somnolence[1], vertigo[1, 2], tremor[1], dizziness[1], postural hypotension[2], coma, confusion[3], stupor[3], headache[2], lethargy[3], difficulty in standing[3]
Eye disorders	Not known	Ocular hyperaemia[3], conjunctival haemorrhage[3, 4]
Respiratory, thoracic and mediastinal disorders	Not known	Cough[2], sore throat[2], dyspnoea[2,3]
Gastrointestinal disorders	Not known	Abdominal pain[1, 2], constipation[1], diarrhoea[1], vomiting[1], nausea[1, 2], epigastric pain[2], fecal incontinence[3]
Hepatobiliary disorders	Not known	Hepatitis acute, hyperbilirubinemia
Skin and subcutaneous tissue disorders	Very rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome

MedDRA System Organ Class	Frequency	Adverse Reaction(s)
Musculoskeletal and connective tissue disorders	Not known	Myalgia[2], arthralgia[2], back pain[3], neck pain[3]
Renal and urinary disorders	Not known	Urinary incontinence[3], haematuria
Reproductive system and breast disorders	Not known	Testicular pain[2], testicular discomfort[2]
General disorders and administration site conditions	Not known	Fever[2], chills[2], diaphoresis[2], asthenia[1, 2], body pain[2], difficulty in walking[3]
Investigations	Not known	Elevated liver enzymes, alanine aminotransferase increased[1], alkaline phosphatase increased[1]

[1]In the treatment of strongyloidiasis
[2]In the treatment of filariasis caused by *Wuchereria bancrofti*
[3]In the treatment of patients who are heavily infected with *Loa Loa*
[4]In the treatment of patients with onchocerciasis

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

28.9 Overdose

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

In cases of 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, edema, headache, vertigo, asthenia, nausea, vomiting, diarrhea and abdominal pain. Other adverse effects that have been reported, include: seizures, ataxia, dyspnea, 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.

29. PHARMACOLOGICAL PROPERTIES

29.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthelmintics, ATC code: P02CF01

Ivermectin is derived from 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 hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite..

Ivermectin also interacts 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 microfilaremia 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 microfilaremia to below 1 % of the pretreatment 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 microfilaremia 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.

34.2 Pharmacokinetic properties

With 12 mg single oral doses of Ivermectin administered as tablets, the mean peak plasma concentration of the major component (H_2B_{1a}) was 46.6 (± 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 absorbed and metabolised in humans, and ivermectin and/or its metabolites are excreted almost exclusively in the feces, whilst less than 1% of the administered dose being excreted in the urine. An *in vitro* study performed on human liver microsomes suggests that cytochrome P4503A4 would be the predominant isoform responsible for the metabolism of ivermectin in liver. The plasma half-life of ivermectin in man is about 12 hours and that of the metabolites is about 3 days.

Preclinical studies suggest that ivermectin has neither the potential to significantly inhibit CYP3A4 (IC50 = 50 μM) or other CYP enzymes (2D6, 2C9, IA2 and 2E1).

39.3 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, fetal 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.

40. PHARMACEUTICAL PARTICULARS

40.1 List of excipients

Microcrystalline cellulose (E460)
Pregelatinised maize starch
Citric acid (E330)
Butylhydroxyanisole
Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blister: 36 months

Bottle: 36 months

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions
Store in the original package in order to protect the product from light.

6.5 Nature and contents of container

1, 4, 8, 10, 20 tablets in aluminium/aluminium blisters.

HDPE bottle containing 250 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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