SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

IVERMECTIN 3 mg, tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 3 mg of ivermectin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

The tablets are round, white or almost white, flat chamfered with a diameter of 5.5 mm and thickness of 2.1 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of intestinal strongyloidiasis (anguillulosis).
- Treatment of suspected or diagnosed microfilaraemia in patients with lymphatic filariasis due to *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.

4.2 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 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 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.

Note for patients treated for scabies

Contact persons, especially family members and partners, should undergo a medical examination as soon as possible, and if necessary should be given prompt antiscabies treatment.

Hygienic measures to prevent reinfection should be taken into account (i. e. keeping fingernails short and clean) and official recommendations regarding the cleaning of clothing and bedding should be closely followed.

Paediatric population
For all indications, safety in children 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.

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.

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).

Cases of neurological toxicity, such as decreased consciousness and coma, have been reported with the use of ivermectin by patients without Loa loa infection. These events usually resolved by supportive measures and by discontinuing ivermectin (see sections 4.8 and 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 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).

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 in association 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.

Precautions for use

Paediatric population

Safety in children 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 interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 potential risk to humans is not known.

Ivermectin should only be used when if strictly necessary.

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 only be given to breastfeeding mothers if the beneficial effect for the mother outweighs the potential risk to the breastfed infant, and treatment of mothers planning to breastfeed their infants should be delayed until 1 week after the child's birth.

4.7 Effects on ability to drive and use machines

It is not known whether ivermectin affects the ability to drive and use machines. The possibility in some patients of side effects such as dizziness, somnolence, vertigo and tremor, which may affect the ability to drive or use machines, cannot be excluded (see section 4.8).

4.8 Undesirable effects

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

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

Cases of neurological toxicity, such as decreased consciousness and coma, have been reported (see sections 4.4 and 4.9).

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, conjunctival haemorrhage,

dyspnoea, urinary and/or faecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor or coma (see section 4.4).

For the treatment of strongyloidiasis, the following adverse reactions have been reported after treatment with ivermectin: 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 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. 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.

4.9 Overdose

It is important to follow the recommended dosages. Cases of impaired consciousness and coma due to overdose with ivermectin have been reported.

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 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 data 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

Pharmacotherapeutic group: Anthelmintics, ATC code: P02CF01.

Ivermectin is derived from avermectins isolated from fermentation broths of *Streptomyces avermitilis*. It binds selectively and with high affinity to glutamate-gated chloride ion channels present in invertebrate nerve and muscle cells. This leads to an increase in cell membrane permeability to chloride ions, with hyperpolarization of the neural or muscle cell, leading to paralysis and death of the parasite.

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 in humans.

In clinical studies in patients with *Wuchereria bancrofti* induced microfilaraemia in Africa, Asia, South America, the Caribbean and Polynesia, a single oral dose of at least 100 μg/kg of ivermectin was shown to reduce microfilaraemia in the week following administration to less than 1% of the pre-treatment value. These studies showed that both the extent and duration of the treatment effect were dose-dependent.

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

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.

The plasma concentration increases with increasing doses in a generally proportional manner. Ivermectin is absorbed and metabolised in the human body. 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. 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.

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 showed toxicity to the central nervous system, as manifested by the appearance of mydriasis, tremors and ataxia at high doses in several species (mice, rats and dogs), as well as vomiting and mydriasis in monkeys. Following administration of repeated doses of ivermectin close or equal to maternotoxic doses, foetal abnormalities (cleft palate) were observed in several animal species (mice, rats, rabbits). From these studies, it is difficult to assess the risk associated with administration of a single low dose. Ivermectin was *in vitro* not genotoxic, nevertheless, no genotoxicity or carcinogenicity *in vivo* data are available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline (E 460)

Pregelatinised maize starch

Butylhydroxyanisole (E 320)

Magnesium stearate (E 470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

4, 8, 10, 12, 16 or 20 tablets in aluminium/aluminium blisters. 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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UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)

PL 47587/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/01/2024

10 DATE OF REVISION OF THE TEXT

11/03/2025