SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ivermectine Aristo 3 mg, tabletten
Ivermectine Aristo 6 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 3 mg of ivermectin.
Each tablet contains 6 mg of ivermectin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

[for 3 mg tablets]
The tablets are white to off white colored, round shaped and biconvex having a diameter of approximately 5 mm.

[for 6 mg tablets]
The tablets are white to off white colored, round shaped, biconvex tablets with a break mark having a diameter of approximately 6 mm.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of gastrointestinal strongyloidiasis (anguillulosis);
- Treatment of diagnosed or suspected 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.

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

4.2 Posology and method of administration

Posology

Treatment of gastrointestinal 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:

[for 3 mg only]

BODY WEIGHT (kg)	DOSE (number of 3 mg tablets)
15 to 24	1
25 to 35	2
36 to 50	3
51 to 65	4
66 to 79	5
≥ 80	6

[for 6 mg only]

BODY WEIGHT (kg)	DOSE (number of 6 mg tablets)
15 to 24	0.5
25 to 35	1
36 to 50	1.5
51 to 65	2
66 to 79	2.5
≥ 80	3

Treatment of microfilaraemia caused by Wucheria 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:

[for 3 mg only]

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	1	2
26 to 44	2	4
45 to 64	3	6
65 to 84	4	8

[for 6 mg only]

BODY WEIGHT (kg)	DOSE when given once every 6 months (number of 6mg tablets)	DOSE when given once every 12 months (number of 6 mg tablets)
15 to 25	0.5	1
26 to 44	1	2
45 to 64	1.5	3
65 to 84	2	4

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:

[for 3 mg only]

HEIGHT (cm)	DOSE when given once every 6 months (number of 3 mg tablets)	DOSE when given once every 12months (number of 3 mg tablets)

90 to 119	1	2
120 to 140	2	4
141 to 158	3	6
> 158	4	8

[for 6 mg only]

HEIGHT (cm)	DOSE when given once every 6 months (number of 6 mg tablets)	DOSE when given once every 12months (number of 6 mg tablets)
90 to 119	0.5	1
120 to 140	1	2
141 to 158	1.5	3
> 158	2	4

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:
- if specific new lesions occur;
- if the parasitological examination is positive at this date.

Profuse and crusting scabies
In these heavily infected forms, a second dose of ivermectin and/or concomitant topical therapy may be necessary within 8 to 15 days 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 paediatric patients weighing less than 15 kg of body weight has not been established.

Elderly patients
Clinical studies with ivermectin did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, treatment of an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Method of administration

Oral use.

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

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.

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* infection. These reactions have generally resolved with supportive care and discontinuation of ivermectin (see sections 4.8 and 4.9).

Limited data indicate that the risk of neurotoxic effects may be increased in patients with reduced P-glycoprotein activity, e.g. loss-of-function mutation in the ABCB1 gene (MDR1).

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).

Paediatric population
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 interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Fertility
Ivermectin had no adverse effects on the fertility in rats up to 3 times the maximum recommended human dose of 200 μg/kg (on a mg/m²/d basis)

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 predictive value of these observations has not been established.
Ivermectin should only be used when strictly indicated.

Breastfeeding
Less than 2% of the administered dose of ivermectin appears in breast milk.
Safety of use has not been established in newborn infants. Ivermectin may only be given to breastfeeding mothers if the expected benefit outweighs the potential risk to the infant.

4.7 Effects on ability to drive and use machines

The effect of on the ability to drive and use machines has not been studied. 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

Tabulated list of adverse reactions

The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1 000 to < 1/100), Rare (≥ 1/10 000 to < 1/1 000), Very rare (< 1/10 000), not known (cannot be estimated from the available data)

System Organ Class	**Frequency**	**Adverse reactions**
Infections and infestations	Not known	Conjunctivitis[d], chorioretinitis[d]
Blood and lymphatic system disorders	Common	Elevated transaminases, leukopenia[b], lymphadenopathy[d]
	Not known	Anaemia[b], lymphadenitis[d]
Immune system disorders	Very rare	Stevens-Johnson syndrome
	Not known	Asthma
Endocrin system disorders	Not known	Excess sweating[c]
Metabolism and nutrition disorder	Common	Anorexia[b,c]
	Not known	Edema[d]
Psychiatric disorders	Common	Somnolence[b]
	Not known	Mental status changes[a], confusion[a], stupor[a]
Nervous system disorders	Common	Dizziness[b], vertigo[b,c,d], tremor[b]
	Rare	Encephalopathy[a]
	Not known	Gait disturbance, coma[a], headache[c,d]
Eye disorders	Not known	Ocular hyperaemia[a], subconjunctival haemorrage[a], iridocyclitis, limbitis[d], keratitis[d], choroiditis[d], anterior uveitis[d], eyelid oedema[d], abnormal sensation in eye[d]
Cardiac disorders	Not known	Tachycardia[d]
Vascular disorders	Not known	Orthostatic hypotension[c,d]
Respiratory, thoracic and mediastinal disorders	Not known	Cough[c], respiratory discomfort[c], exacerbation of asthma[d], sore throat[c], dyspnoea[a]
Gastrointestinal disorders	Common	Abdominal pain[b,c], abdominal pain upper, diarrhoea[b,d], nausea[b,c,d], vomiting[b,d], epigastric pain[c], faecal incontinence[a]
	Not known	Anal incontinence, constipation[b], oropharyngeal pain
Hepatobiliary disorders	Not known	Hypereosinophilia[b], liver disorder, hepatitis acute, hyperbilirubinemia, liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Pruritus[d], rash[d], urticaria[d]
Musculoskeletal and connective tissue disorders	Not known	Back pain[a], neck pain[a], myalgia[c,d], arthralgia[c,d], chills[c]
Renal and urinary disorders	Not known	Urinary incontinence[a]
Reproductive system and breast disorders	Not known	Hematuria, testicular pain[c]

General disorders and administration site conditions	Not known	Dysstasia[a], lethargy[a], asthenia[b,c,d], pyrexia[c,d], hyperhidrosis, discomfort, diffuse pain[c], feelings of weakness[c], walking difficulty[a]
Investigations	Not known	Liver enzyme elevations (ALAT/ALP)[b]
Injury, poisoning and procedural complications	Very rare	Toxic epidermal necrolysis

[a]: Patients infected with *Loa loa*
[b]: Patients with intestinal strongyloidiasis
[c]: Patients with *Wuchereria bancrofti* filariasis
[d]: Patients infected with *Onchocerca volvulus*

Description of selected adverse reactions
Patients infected with *Loa loa*: 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*.

Patients with scabies: transient exacerbation of pruritus may be observed at the start of treatment.
Patients infected with *Ascaris*: Observations of adult *Ascaris* expulsion have been described following ingestion of ivermectin.

Patients with onchocerciasis: Onset of conjunctival haemorrhage has been reported.

Paediatric population
A similar safety profile was observed in pediatric patients ages 6 to 13.
The safety and efficacy of ivermectin in children weighing less than 15 kg have not been established. The use of ivermectin is not recommended in young children (e. g. those weighing less than 15 kg or younger than 2 years of age) in part because the blood-brain barrier may be less developed than in older patients.

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 the national reporting system listed in Appendix V.

4.9 Overdose
It is important to follow the recommended doses.
Cases of loss of consciousness and coma have been reported due to ivermectin overdose.
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

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

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. Standard studies conducted *in vitro* (Ames test, mouse lymphoma TK assay) did not show any genotoxicity. Nevertheless, no genotoxicity or carcinogenicity studies were conducted *in vivo*.

Environmental risk assessment studies have shown that ivermectin may pose a risk for the aquatic compartment, the groundwater compartment, the sediment compartment and the soil compartment. It is very toxic to aquatic organisms and has the potential to be very persistent in the environment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline (E 460)
Citric acid (E 330)
Butylhydroxyanisole (E 320)
Starch, pregelatinised
Silica, colloidal anhydrous (E 551)
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.
Store in the original package in order to protect the product from light.

6.5 Nature and contents of container

[for 3 mg only]
Ivermectin Aristo 3 mg tablets are packed in blister cards consisting of OPA/Aluminium/PVC foil sealed with a heatseal lacquered Aluminium foil.

[for 6 mg only]
Ivermectin Aristo 6 mg tablets are packed in blister cards consisting of OPA/Aluminium/PVC foil sealed with a heatseal lacquered Aluminium foil.

Pack sizes:
- *[for 3 mg only]* 4, 6, 8, 10 tablets
- *[for 6 mg only]* 2, 4, 12 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of according to local requirements.

7. MARKETING AUTHORISATION HOLDER

Aristo Pharma GmbH
Wallenroder Straße 8-10 13435 Berlin
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

Ivermectine Aristo 3 mg, tabletten	RVG 133954
Ivermectine Aristo 6 mg, tabletten	RVG 133955

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 1 december 2025

10. DATE OF REVISION OF THE TEXT