ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ivermectin/Albendazole 9 mg/400 mg orodispersible tablets
Ivermectin/Albendazole 18 mg/400 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 9 mg ivermectin and 400 mg albendazole.
Each orodispersible tablet contains 18 mg ivermectin and 400 mg albendazole.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet (tablet).

Ivermectin/Albendazole 9 mg/400 mg orodispersible tablets
Round, white to almost white, orodispersible tablets of approximately 16 mm of diameter, debossed with "9/400" on one side.

Ivermectin/Albendazole 18 mg/400 mg orodispersible tablets
Round, white to almost white, orodispersible tablets of approximately 16 mm of diameter, debossed with "18/400" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ivermectin/Albendazole orodispersible tablets are indicated in adults, adolescents and children ≥ 5 years of age for the treatment of:

- Soil-transmitted helminth infections, caused by one or more of the following parasites (see section 5.1): hookworm (*Ancylostoma duodenale, Necator americanus*), roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) and *Strongyloides stercoralis.*
- Proven or suspected microfilaraemia in patients with lymphatic filariasis caused by *Wuchereria bancrofti.*

Ivermectin/albendazole should be used in accordance with official guidance, which may include guidance provided by the World Health Organization and public health authorities.

4.2 Posology and method of administration

Therapy should be initiated by a physician or health care professional experienced in the management of helminth infections.

Posology

Individual treatment (outside the framework of a mass drug administration)

Adults, adolescents and children aged 5 years and older with a body weight of:
15 kg to < 45 kg: one single oral dose of 9 mg/400 mg ivermectin/albendazole orodispersible tablet for 3 consecutive days

≥ 45 kg: one single oral dose of 18 mg/400 mg ivermectin/albendazole orodispersible tablet for 3 consecutive days

Alternatively, height-based doses are:
105 cm to 140 cm: one single oral dose of 9 mg/400 mg ivermectin/albendazole orodispersible tablet for 3 consecutive days
≥ 141 cm: one single oral dose of 18 mg/400 mg ivermectin/albendazole orodispersible tablet for 3 consecutive days

Mass drug administration

For mass drug administration (MDA), the recommended dose is 9 mg/400 mg (15 kg to < 45 kg, 105 cm to 140 cm) or 18 mg/400 mg (≥ 45 kg, ≥ 141 cm) ivermectin/albendazole orodispersible tablet given as one single oral dose once a year. If required, the dose may be given twice a year at 6-monthly intervals in line with national treatment plans.

Paediatric population
No data are available for the use of Ivermectin/Albendazole orodispersible tablets in children < 5 years of age as this age group has not been investigated in the relevant studies.
For all indications, safety in paediatric patients weighing less than 15 kg body weight has not been established.

Elderly
Experience with albendazole in elderly patients ≥65 years is limited. Reports show that no dose adjustment is required.
Clinical studies with ivermectin did not include sufficient numbers of subjects ≥ 65 years 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 elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see section 4.4).

Renal impairment
No dose adjustment is required in patients with renal impairment.

Hepatic impairment
Ivermectin/Albendazole orodispersible tablets should be used with caution in patients with known hepatic impairment (see sections 4.4 and 5.2).

Method of administration

Oral use.
The orodispersible tablet is fragile and should be taken immediately upon opening the blister with dry hands. It should be placed on the tongue, where it will rapidly dissolve upon contact with saliva. It can be taken without water or can be dispersed in at least 20 mL of water and the resulting suspension completely taken.

The dose should be taken with or after a meal (see section 5.2).

The dissolved orodispersible tablet may also be given through an enteral (nasogastric or gastric) feeding tube (see section 6.6).

4.3 Contraindications

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

Ivermectin/Albendazole orodispersible tablets are contraindicated for use in MDA campaigns in pregnancy and in women who intend to become pregnant. For use in individual therapy (outside the scope of a mass drug administration), see section 4.6.

Treatment with Ivermectin/Albendazole orodispersible tablets is contraindicated in patients with high *Loa loa* microfilaria and for MDA settings in *Loa loa* endemic regions, unless a feasible and validated risk mitigation strategy can be put in place which should follow WHO recommendations or relevant national guidelines for safe use in these settings.

4.4 Special warnings and precautions for use

Ivermectin

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.

Other

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 alone 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 (see section 4.3).

CNS adverse experiences (encephalopathies) have been rarely reported in patients treated with ivermectin and co-infected with a high number of microfilariae of *Loa loa*. For individual treatment (outside the scope of a mass drug administration) in *Loa loa* endemic areas, special measures (e.g. pre-treatment diagnostic tests such as Giemsa-stained thin or thick blood smears, any validated quantifiable *Loa loa* diagnostic test available in the country, knowledge of regional *Loa loa* prevalence, monitoring of patients for serious CNS adverse events) should be taken before any treatment with ivermectin. Generally, patients with a high *Loa Loa* microfilaria must not be given ivermectin (see section 4.3). Given the limited access to diagnostic tests in MDA settings, MDA treatment with ivermectin in *Loa Loa* endemic areas is contraindicated unless feasible and validated risk mitigation strategies are put in place (see section 4.3). In cases where MDA with ivermectin is deemed unsafe, alternative treatment strategies are necessary. Overall, monitoring patients for serious CNS symptoms is essential to prevent adverse effects and affected patients should be referred and managed appropriately (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. This toxicity might be connected to a reduced P-glycoprotein activity (e.g. due to a genetic polymorphism in the ABCB1 gene (MDR1)) resulting in increased blood levels of ivermectin and subsequently diffusion into the CNS. These events have generally resolved with supportive care and the discontinuation of 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.

Systematic 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 active substance (see section 4.3).

Albendazole

Since albendazole is rapidly degraded in the liver to its primary pharmacologically active metabolite albendazole sulfoxide, it can be assumed that hepatic impairment has a significant effect on the pharmacokinetics of albendazole sulfoxide (see sections 4.2 and 5.2).

During treatment with albendazole mild to moderately elevated hepatic enzymes can occur which usually return to normal after discontinuation of treatment. Cases of hepatitis have also been reported (see section 4.8).

Furthermore, patients with hepatic disease appear to be more susceptible to myelosuppression by albendazole leading to pancytopenia, aplastic anaemia, agranulocytosis and leukopenia (see section 4.8).

In patients receiving Ivermectin/Albendazole orodispersible tablets as an individual therapy (outside the scope of a mass drug administration), hepatic function tests should be performed before starting and at regular intervals during treatment. If hepatic enzymes increase significantly (≥ 2 x ULN), treatment should be discontinued. Retreatment may be considered when hepatic enzymes have returned to normal, but patients should be monitored carefully and at shorter intervals. Patients presenting with abnormal hepatic function tests (transaminses) before starting treatment, should be closely monitored and therapy discontinued if the enzyme values are significantly increased or the blood cell counts are declining to a clinically significant extent (see section 4.8).

If in MDAs access to liver function tests is limited the patient's history of liver disease, heavy alcohol consumption, or use of hepatotoxic drugs should at least be assessed and the patient monitored for any clinical signs of hepatic adverse reactions, including jaundice, dark urine, right upper quadrant abdominal pain, ascites or unexplained fatigue, particularly in patients with risk factors such as pre-existing liver disease or co-administration of other medicinal products.

To avoid treatment during pregnancy, please refer to sections 4.3 and 4.6.

In patients treated with albendazole, an existing neurocysticercosis can be seen, especially in areas with pronounced taeniasis infection. Neurological symptoms may occur in these patients, e.g., seizures, increased intracranial pressure, or focal symptoms resulting from an inflammatory reaction caused by the death of the parasites in the brain. The symptoms may occur shortly after the treatment. Immediate treatment with corticosteroids and anticonvulsants should be initiated.

In rare cases neurocysticercosis may affect the retina. Patients receiving Ivermectin/Albendazole orodispersible tablets for individual therapy (outside the scope of a mass drug administration), should be examined for retinal lesions prior to treatment.

Paediatric population

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

Special population
Ivermectin/Albendazole orodispersible tablets should be used with caution in elderly patients and patients with known hepatic impairment (see above and sections 4.2 and 5.2).

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per orodispersible tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Ivermectin
Ivermectin is a substrate of CYP3A4, substrate and inhibitor of P-gp and MDR1 protein (MRP), and an inhibitor of Breast Cancer Resistance protein (BCRP) transporter. Interactions may occur if co-administered with other active substances that are potent inhibitors/inducers of CYP3A4 enzyme and of MDR1 (P-gp), BCRP or MRP transporters, or when polymorphisms of the drug transporters and CYP3A4 exist.

CYP3A4 inhibitors such as levamisole, clarithromycin, ketoconazole, ciclosporin, verapamil, and diltiazem may result in increased levels of ivermectin.

Ivermectin has also been shown to enhance GABA effects and/or act as a GABA receptor agonist. Active substances that also increase GABA activity such as alcohol, benzodiazepines, and barbiturates have the theoretical potential to increase ivermectin neurotoxicity.

Concomitant intake of orange juice also decreases the exposure to ivermectin, possibly due to inhibition of certain drug transporters.

Post-marketing reports of increased INR (International Normalised Ratio) have been rarely reported when ivermectin was co-administered with warfarin, probably due to interference with vitamin K metabolism. Patients should be monitored for efficacy and safety and may require alternative therapies.

Albendazole
Inducers, inhibitors or substrates of flavin-containing monooxygenase (FMO), CYP3A4 and CYP1A2, and in parts CYP1A1 bear the potential for clinically relevant interactions with albendazole and/or its metabolites.

Pharmacokinetic interactions were reported for the following: concomitant use of albendazole with cimetidine, praziquantel and dexamethasone increases the plasma concentration of the active metabolite of albendazole in plasma. Concomitant intake of grapefruit juice also increases the exposure to albendazole.

Ritonavir, phenytoin, carbamazepine, phenobarbital, and levamisole may possibly reduce the plasma concentrations of the active metabolite of albendazole, albendazole sulfoxide. The clinical relevance of this is unknown, but may result in reduced efficacy, especially in the treatment of systemic helminth infections. Patients should be monitored for efficacy and safety and may require alternative therapies.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

In order to exclude pregnancy, women of childbearing potential should be tested before starting treatment with Ivermectin/Albendazole orodispersible tablets.

Because of the teratogenic properties of albendazole (see section 5.3), women of childbearing potential should use effective contraception shortly before, during, and up to one month after treatment with Ivermectin/Albendazole orodispersible tablets for both individual treatment (outside the scope of a mass drug administration) and MDA campaigns.

Pregnancy

Limited data on 300 pregnant women indicate no adverse effects after ivermectin use. 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.

Limited data on 194 pregnant women from an open-label randomised study indicate no adverse effects after albendazole use. Studies in animals have shown reproductive toxicity (see section 5.3). However, the potential risk for humans is unknown.

An open-label randomised study showed no severe adverse effects in 199 women receiving combined ivermectin and albendazole for treatment of STH infections in the second trimester of pregnancy.

Individual therapy (outside the scope of a mass drug administration)
For the individual therapy (i.e. outside the scope of a mass drug administration) Ivermectin/ Albendazole orordispersible tablets is not recommended especially during the first trimester of pregnancy. It should only be used during pregnancy if the clinical condition of the woman requires treatment with albendazole and ivermectin.

Mass drug administration
Because of the teratogenic properties of albendazole, the use of Ivermectin/Albendazole orordispersible tablets is contraindicated in the framework of a mass drug administration campaign in pregnant women and in women who intend to become pregnant (see section 4.3).

Breast-feeding

Less than 2% of the administered dose of ivermectin appears in human milk, however the safety in newborn infants has not been established.

It is unknown whether albendazole/metabolites are excreted in human milk. Insufficient data regarding breastfeeding are available in humans or animals. A risk to the newborns/infants cannot be excluded.

Individual therapy (outside the scope of a mass drug administration)
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Ivermectin/Albendazole orordispersible tablets therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Mass drug administration
In mass administration programmes for community suppression, women who are breast-feeding should not be given ivermectin contained in Ivermectin/Albendazole orodispersible tablets during the first week after giving birth.

Fertility

There are no data on the effects of ivermectin on human fertility. Ivermectin had no adverse effects on the fertility in rats (see section 5.3).

There are no data on the effects of albendazole on human fertility. Animal studies indicate no effects of albendazole on female and male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Ivermectin
It is not known if ivermectin has an influence on the ability to drive and use machines. Possibile side effects such as dizziness, somnolence, vertigo and tremor may affect some patients' ability to drive or use machines (see section 4.8).

Albendazole
Effects on the ability to drive or use machines have not been observed. However, it should be taken into account that dizziness has been reported after the use of albendazole (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
The following adverse reactions have been observed in clinical studies conducted with the fixed-dose combination product Ivermectin/Albendazole orordispersible tablets and the individual active substances albendazole and ivermectin.

The most serious adverse events known from the literature for ivermectin are encephalopathy (in patients also heavily infected with *Loa loa*), toxic epidermal necrolysis, and Stevens-Johnson syndrome. The most serious adverse events known for albendazole are hepatotoxicity and myelosuppression.

ALIVE study (Phase 2/3 study)
The safety of the FDC has been studied in an adaptive Phase 2/3 single-blinded, randomised, multicentre, parallel-group, active-controlled, superiority study investigating a single dose-single day (FDC SD) or single dose 3-day (FDC x3) regimen of the albendazole/ivermectin co-formulation vs. an albendazole single formulation. Study drug-related TEAEs (treatment-emergent adverse event) were reported in ≤ 20% of participants overall in both study phases and the majority were mild or moderate in severity. No treatment-emergent serious adverse event (SAE) and no TEAE leading to study drug discontinuation occurred in either study phase. Abdominal pain was the most frequently reported TEAE in both study phases (Phase 2 part: 7.8%, n=4 for FDC SD and 13.0%, n=7 for FDC x3; Phase3 part: 12.4%, n=41 for FDC SD and 11.5%, n=37 for FDC x3). The study was however not powered to statistically analyse safety.

Tabulated list of adverse reactions
Undesirable effects are listed according to System Organ Classes and their frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

Adverse drug reactions as reported for the FDC in Phase 1 and Phase 2/3 studies and for albendazole and ivermectin single substances (observed in the ALIVE study and from literature)

Blood and lymphatic system disorders	
Uncommon	Leucopenia[2], anaemia
Very rare	Pancytopenia[2], aplastic anaemia[2], agranulocytosis[2]
Not known	Transient eosinophilia, lymphadenitis, adenopathies, lymph node enlargement or tenderness
Immune system disorders	
Uncommon	Hypersensitivity reactions including skin rash, itching and urticaria[3]
Psychiatric disorders	

Not known	Mental status changes
Nervous system disorders	
Very common	Headache
Common	Dizziness
Uncommon	Somnolence Existing symptoms may worsen, or new neurological disorders may occur (epilepsy, meningitis, hemiplegia, conspicuous fatigue), presyncope
Rare	Encephalopathy
Not known	Depressed level of consciousness (neurotoxic effect of ivermectin), vertigo, tremor, orthostatic hypotension, coma (neurotoxic effect of ivermectin), confusion, stupor, lethargy, difficulty in standing/walking, paraesthesia
Eye disorders	
Common	Vision blurred, punctate opacity
Uncommon	Conjunctivitis, limbitis
Not known	Ocular hyperaemia, conjunctival haemorrhage, subconjunctival haemorrhage, abnormal sensation in the eyes, eyelid oedema, anterior uveitis, keratitis, chorioretinitis or choroiditis
Cardiac disorders	
Not known	Tachycardia
Vascular disorders	
Not known	Hypotension
Respiratory, thoracic and mediastinal disorders	
Common	Cough
Uncommon	Asthma exacerbation,
Not known	Dyspnoea, sore throat
Gastrointestinal disorders	
Very common	Abdominal pain
Common	Diarrhoea$^{\infty}$, nausea, vomiting, parasitic gastroenteritis
Uncommon	Abdominal distension, abdominal cramp, constipation, odynophagia, flatulence, dyspepsia, stomatitis
Not known	Faecal incontinence, anorexia, epigastric pain
Hepatobiliary disorders	
Very common	Elevated liver enzymes[1]
Uncommon	Hepatitis[2]
Not known	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Common	Reversible hair loss (thinning of hair, moderate hair loss)[2], acne
Uncommon	Pruritus, rash, rash pruritic, itchiness

Very rare	Erythema multiforme, Stevens-Johnson-Syndrome, toxic epidermal necrolysis
Not known	Urticarial rash, contact dermatitis
Musculoskeletal and connective tissue disorders	
Uncommon	Arthralgia
Rare	Bone pain
Not known	Myalgia, back pain, neck pain
Renal and urinary disorders	
Rare	Proteinuria
Not known	Urinary incontinence, haematuria
Reproductive system and breast disorders	
Not known	Testicular pain and discomfort
General disorders and administration site conditions	
Common	Pyrexia
Uncommon	Epistaxis, decreased appetite
Not known	Oedema, including peripheral and facial oedema, asthenia, fatigue, chills, diffuse pain, increased sweating
Investigations	
Uncommon	Blood creatine phosphokinase increased

[1] Frequency "rare" in short-term albendazole treatment, mild to moderate elevation "very common" in longer-term albendazole treatment
[2] For albendazole seen only in longer-term treatment
[3] For albendazole "rare" in short-term treatment and "uncommon" in longer-term treatment

Description of selected adverse reactions

Ivermectin

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

Rarely, patients who are also heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy following treatment with ivermectin. In these patients, the following adverse 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 (neurotoxic effect of ivermectin). For individual treatment (outside the scope of a mass drug administration) in *Loa Loa* endemic areas, specific measures like pre-treatment diagnostic tests, validated quantifiable Loa loa diagnostic tests available in the country, knowledge of regional *Loa loa* prevalence, and monitoring of patients for serious CNS adverse events should be taken before any treatment with ivermectin and affected patients should be referred and managed appropriately (see section 4.4). Generally, ivermectin must not be given to patients with high *Loa Loa* microfilaria and for MDA settings in *Loa Loa* endemic areas unless a feasible and validated risk mitigation strategy can be put in place (see section 4.3). In cases where MDA with ivermectin is deemed unsafe, alternative treatment strategies are necessary.

Paediatric patients

Parents should be instructed to seek immediate medical care if the child shows any of the following symptoms: confusion, tremors, unusual drowsiness or irritability, swelling of the face or eyes, severe abdominal pain, persistent vomiting, or fever above 38 °C that does not subside.

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

Ivermectin
Symptoms of overdose
Cases of accidental overdose with ivermectin have been reported, but none has resulted in fatalities. In accidental intoxication with unknown quantities of veterinary formulations of ivermectin in humans (oral use, injectable, cutaneous use), the following symptoms have been reported: rash, contact dermatitis, oedema, headache, vertigo, asthenia, nausea, vomiting, diarrhoea and abdominal pain. Other effects have also been observed including convulsions, ataxia, dyspnoea, paraesthesia and urticaria. Reduced consciousness and coma might also be observed as a neurotoxic effect of ivermectin.

Treatment of overdose
Symptomatic treatment and surveillance in a medical setting with fluid replacement and hypertensive treatment, if necessary. Although there are no specific studies available, it is advisable to avoid the combination of GABA agonists in the treatment of accidental intoxication due to ivermectin.

Albendazole
Albendazole has only a low acute toxicity. So far, no reports of intoxications are available. Specific antidotes are not known.

Treatment of overdose
The treatment of overdose should be performed according to the clinical manifestation or according to recommendations from the national toxicology centre, if available.

Since more attention should be given to possible undesirable effects after intoxication, monitoring of the blood count and the liver values are recommended (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthelmintics, antinematodal agents, benzimidazole derivatives, ATC code: P02CA53

Mechanism of action

If co-administered, ivermectin and albendazole act synergistically to enhance parasite clearance. Ivermectin targets the parasite’s nervous and muscular systems, causing paralysis by increasing chloride ion permeability, while albendazole disrupts cellular function by blocking tubulin polymerisation, which is essential for parasite metabolism and energy production. This dual approach immobilises and kills the parasite through complementary pathways, effectively enhancing the treatment's overall efficacy against a wide range of helminths.

Clinical efficacy

Ivermectin/Albendazole orodispersible tablets

One randomised, controlled adaptive Phase 2/3 study (ALIVE) investigated the efficacy of ivermectin/albendazole FDC (9 mg/400 mg or 18 mg/400 mg) administered either as single dose (FDC SD) or as a single dose on 3 consecutive days (FDC x 3) for the treatment of soil-transmitted helminth infections in paediatric patients (≥ 5 years of age and weighing at least 15 kg) and young adults in Kenya, Mozambique and Ethiopia. It was demonstrated that the FDC was significantly more effective for treatment of *T. trichiura* infections than albendazole alone:the cure rate (CR) was 97.2% [95% CI: 95.2, 99.3]) in the FDC x 3 arm and 82.9% [95% CI: 78.2, 87.5]) in the FDC SD arm compared to 35.9% [95% CI: 27.7, 44.1]) in the albendazole arm (CR differences 61.3% and 47.2%, respectively [p <0.0001 for both comparisons]). The FDC given as a single dose on 3 consecutive days was also more effective for curing hookworm infection than albendazole. The efficacy of the FDC for curing *S. stercoralis* infections was considered inconclusive due to the small sample size.

5.2 Pharmacokinetic properties

Ivermectin

Absorption and biotransformation

With a single oral dose of 12 mg of ivermectin administered as tablet the mean peak plasma concentration of the main compound (H_2B_{1a}) was 46.6 (±21.9) ng/mL at approximately 4 hours after dosing. Plasma concentration increases with increasing doses in an approximately proportional manner. Ivermectin is absorbed and metabolised in the human body.

Intake of Ivermectin/Albendazole orodispersible tablets results in the delivery of ivermectin doses between 200 and 600 µg/kg, depending on body weight. In healthy volunteers, administration of ivermectin with a high-fat meal resulted in an up to 2.5-fold increase in bioavailability relative to the fasted state. Under light meal conditions, ivermectin in the orodispersible tablets was bioequivalent to the ivermectin brand comparator. Overall, administration with food has no clinically relevant impact on the safety and efficacy of Ivermectin/Albendazole orodispersible tablets.

Elimination

Ivermectin and/or its metabolites are excreted almost exclusively in the faeces, with less than 1% of the administered dose excreted in the urine. An *in vitro* study in human liver microsomes suggests that CYP3A4 is the predominant isoform responsible for the hepatic metabolism of ivermectin. In humans, the plasma half-life of ivermectin is approximately 12 hours and that of its metabolites is approximately 3 days.

Preclinical studies suggest that ivermectin, used at therapeutic oral doses, has neither the potential to significantly inhibit CYP3A4 (IC_{50} = 50 µM) nor other CYP enzymes (2D6, 2C9, 1A2 and 2E1).

Albendazole

Absorption and biotransformation

Albendazole is lipophilic and is therefore poorly absorbed (<5%) after oral administration. Albendazole is subject to a high first-pass metabolism in the liver and is usually not detectable in plasma. It is rapidly metabolised to the main active metabolite albendazole sulfoxide, which is responsible for the anthelmintic activity. The systemic availability increases approximately 5 times if albendazole is administered with a high fat meal. Emulsified fat (e.g. in liquid food), on the other hand, does not have an improving effect on availability. After a single oral administration of 400 mg albendazole taken with breakfast (fat content about 40 g), the maximum plasma concentration of albendazole sulfoxide was between1.8 to 6.0 µmol/L.

The plasma half-life of albendazole sulfoxide is 8.5 hours.

Distribution
The primary metabolite albendazole sulfoxide is 70% bound to plasma protein. It is widely distributed throughout the body and detectable e.g. in urine, bile, liver, and cerebrospinal fluid.

Elimination
Albendazole and its metabolites are eliminated mainly via the bile and only to a small extent via the urine.

Ivermectin/Albendazole orodispersible tablets
Population pharmacokinetics of the FDC product was extensively evaluated and data consolidated from the Phase 1 PK study in healthy adult subjects (BLCL-IVA-EU-01) as well as from the Phase 2 part of the ALIVE study in children and young adults with STH infection. The dose regimens in ALIVE study was designed to achieve similar albendazole and ivermectin PK exposure in paediatrics and young adults as the adult healthy subjects in the BLCL-IVA-EU-01 study treated with 400 mg of single substance albendazole brand comparator and 18 mg of single substance ivermectin brand comparator.

Albendazole sulfoxide PK was described using a 2-compartmental model with 1st-order absorption. Typical apparent clearance (CL/F) and apparent volume of the central compartment (Vc/F) for an adult male subject were estimated to be 82.3 L/h and 845 L, respectively. Elimination half-life was 15.5 hours. Bioavailability of albendazole in the FDC formulation was 78.5% of the comparator albendazole single substance brand medicinal product. Albendazole sulfoxide clearance and volume increased with body weight. Female subjects were 10% lower in CL/F. Age, race, and population (healthy vs STH infected) had no impact on the PK after accounting for the difference in body weight.

Ivermectin (H2B1a) PK was described using a 2-compartmental model. Typical CL/F and Vc/F for an adult subject were estimated to be 16.4 L/h and 48.1 L, respectively. Elimination half-life was 43.6 hours. Bioavailability of ivermectin H2B1a in the FDC formulation was 116% of the comparator ivermectin single substance brand medicinal product. Ivermectin clearance and volume increased with body weight. The AUC for ivermectin was lower in participants under 30 kg of weight compared with participants ≥ 30 kg. Sex, age, race, and infection status (healthy vs STH infected) had no impact on the PK after accounting for the difference in body weight.

Special populations
Paediatric population
Analyses across studies evidenced that AUC for albendazole and ivermectin in paediatric or young adults with STH infections (FDC 18 mg/400 mg (≥30 kg) or FDC 9 mg/400 mg (<30 kg)) was comparable to adult healthy subjects treated with 400 mg albendazole brand or 18 mg ivermectin brand.

Elderly
Although no studies have investigated the effect of age on the pharmacokinetics of albendazole sulphoxide, data from 26 patients with echinococcal cysts suggest that the pharmacokinetics of these patients (aged 79 years) are similar to those of young healthy people.

Renal impairment
The pharmacokinetics of albendazole (respectively albendazole sulfoxide) and ivermectin in patients with impaired renal function have not been studied. However, since renal elimination of albendazole and ivermectin is negligible, it is unlikely that clearance of these compounds would be altered in these patients. No dose adjustment is required in patients with renal impairment (see section 4.2).

Hepatic impairment
The pharmacokinetics of albendazole (respectively albendazole sulfoxide) and ivermectin in patients with impaired hepatic function have not been studied. In patients with evidence of extrahepatic obstruction, the systemic availability of albendazole sulfoxide was increased 7-fold. However,

Ivermectin/Albendazole orodispersible tablets should be used with caution in patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

No toxicity studies with the combination product of ivermectin and albendazole have been conducted.

Ivermectin
Single dose toxicity studies revealed central nervous system toxicity evidenced by mydriasis, tremors, and ataxia at high doses in several animal species (mice, rats and dogs) as well as emesis and mydriasis (monkeys). After administration of repeated doses of ivermectin close or equal to maternotoxic doses, foetal abnormalities (cleft palate) have been 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. *In vitro* ivermectin was not genotoxic,however, *in vivo* genotoxicity and carcinogenicity data are lacking. Ivermectin had no adverse effects on the fertility in rats in studies at repeated doses of up to 600 micrograms/kg (on a mg/m^2/day basis).

Albendazole
Albendazole has a low acute toxicity. Symptoms included weight loss, clonic convulsion, impact on respiration and diarrhoea.
Studies for up to 6 months in mice, rats and dogs revealed the haematopoietic system and the liver as the target organs of toxicity. A cell transformation test on BALB/3T3 cells *in vitro* was weakly positive only after previous metabolic activation. Non-clinical data for albendazole reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenic potential.

Albendazole has shown to cause embryotoxicity and skeletal malformations in pregnant rats and rabbits. The teratogenic response in the rat was shown at oral doses of 10 and 30 mg/kg/day during gestation days 6 to 15, and in pregnant rabbits at oral doses of 30 mg/kg/day administered during gestation days 7 to 19. In the rabbit study, maternal toxicity (33% mortality) was noted. Albendazole did not affect male or female fertility in the rat at an oral dose level of 30 mg/kg/day.

Environmental risk assessment (ERA)
Environmental risk assessment studies have shown that both, albendazole and ivermectin may pose a risk for the aquatic compartment and ivermectin has the potential to be persistent in the environment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium (E468)
Povidone
Mannitol (E421)
Butylhydroxyanisole (E320)
Citric acid (E330)
Mango flavour *(consisting of: flavouring preparations, flavouring substance, natural flavouring substance, maltodextrin, gum arabic (E414), triacetin (E1518), propylene glycol (E1520))*
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10, 30, 60 and 80 orodispersible tablets in PA/Alu/PVC/Alu and OPA/Alu/desiccant/Alu blister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Administration via enteral feeding tube
The prescribed dose of Ivermectin/Albendazole orodispersible tablets may be dissolved in a syringe with 5 mL of water by gently rotating and administered via an enteral feeding tube10 FR (French catheter scale). Follow the manufacturer's instructions for the feeding tube to administer the medicinal product. To ensure adequate dosing, after administration of the suspension, the enteral feeding tube must be flushed with 35 mL water.

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 in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

Laboratorios Liconsa, S.A.
Calle Dulcinea S/N
Alcalá de Henares
28805 Madrid
Spain

8. SCIENTIFIC OPINION AUTHORISATION NUMBER(S)

9. DATE OF SCIENTIFIC OPINION /RENEWAL OF THE SCIENTIFIC OPINION

Date of scientific opinion:

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Laboratorios Liconsa S.A.
Avda. Miralcampo, Nº 7 Pol.Ind. Miralcampo
19200 Azuqueca de Henares, Guadalajara
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION

- **Periodic safety update reports (PSURs)**

The scientific opinion holder shall submit the first periodic safety update report for this product within 6 months after the scientific opinion. Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every 6 months until otherwise agreed by the CHMP.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The scientific opinion holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the scientific opinion and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

{CARTON BOX}

1. NAME OF THE MEDICINAL PRODUCT

Ivermectin/Albendazole 9 mg/400 mg orodispersible tablets
Ivermectin/Albendazole 18 mg/400 mg orodispersible tablets

ivermectin/albendazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains 9 mg ivermectin and 400 mg albendazole.
Each orodispersible tablet contains 18 mg ivermectin and 400 mg albendazole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet.

10 tablets
30 tablets
60 tablets
80 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
The orodispersible tablet is fragile and should be removed from the blister with dry hands and taken immediately once removed from the blister.
Read the package leaflet before use.

Patient groups
Ivermectin/Albendazole 9 mg/400 mg orodispersible tablets

Height: 105 cm to 140 cm

Weight: 15 kg to less than 45 kg

Age: 5 years and older

Do not use for MDA during pregnancy or with the intention of becoming pregnant. (Use not recommended for individual therapy)

Ivermectin/Albendazole 18 mg/400 mg orodispersible tablets

Height: 141 cm and higher

Weight: 45 kg and more

Age: 5 years and older

Do not use for MDA during pregnancy or with the intention of becoming pregnant. (Use not recommended for individual therapy)

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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 in accordance with local requirements.

11. NAME AND ADDRESS OF THE SCIENTIFIC OPINION HOLDER

Laboratorios Liconsa, S.A.
Calle Dulcinea S/N
Alcalá de Henares
28805 Madrid
Spain

12. SCIENTIFIC OPINION AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{ALU/ALU BLISTER}

1. NAME OF THE MEDICINAL PRODUCT

Ivermectin/Albendazole 9 mg/400 mg orodispersible tablets
Ivermectin/Albendazole 18 mg/400 mg orodispersible tablets

ivermectin/albendazole

2. NAME OF THE SCIENTIFIC OPINION HOLDER

Laboratorios Liconsa, S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ivermectin/Albendazole 9 mg/400 mg orodispersible tablets
Ivermectin/Albendazole 18 mg/400 mg orodispersible tablets

ivermectin/albendazole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, health care provider or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, health care provider or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ivermectin/Albendazole orodispersible tablets are and what they are used for

Ivermectin/Albendazole orodispersible tablets contain the medicines ivermectin and albendazole. Ivermectin/Albendazole orodispersible tablets is a combination of medicines (anthelmintics) which is used for infections caused by some parasites.

Ivermectin/Albendazole orodispersible tablets are used in adults, adolescents and children 5 years and older to treat

- Soil-transmitted infections of your intestines caused by:
  - the hookworms "*Ancylostoma duodenale"* and "*Necator americanus"* (ancylostomiasis and necatoriasis)
  - a type of roundworm called "*Ascaris lumbricoides"* (ascariasis)
  - the whipworm "*Trichuris trichiura"* (trichuriasis)
  - a type of roundworm called "*Strongyloides stercoralis*" (strongyloidiasis)

- Proven or suspected microfilaraemia in patients with lymphatic filariasis caused by *Wuchereria bancrofti*

Ivermectin/Albendazole orodispersible tablets will not stop you from getting one of these infections. Ivermectin/Albendazole orodispersible tablets should only be taken when your doctor has proven or thinks you have a parasite infection.

2. What you need to know before you take Ivermectin/Albendazole orodispersible tablets

Do not take Ivermectin/Albendazole orodispersible tablets if
- you are allergic to ivermectin and albendazole or any of the other ingredients of this medicine (listed in section 6).
- you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking ivermectin

- you are pregnant, think you may be pregnant or intend to become pregnant in the framework of a mass drug administration. For the use in individual therapy (outside the scope of mass drug administration) see "Pregnancy, breast-feeding and fertility" below).
- you have an infection with a high load of *Loa loa* (*Loa loa* microfilaria).
- Ivermectin/Albendazole orodispersible tablets are used for mass treatment programs in *Loa loa*-affected areas.
  Your doctor will decide if you can be treated as long as adequate risk minimisation measures can be put in place for safe use in these settings.

Warnings and precautions
Talk to your doctor, health care provider or pharmacist before taking Ivermectin/Albendazole orodispersible tablets.

In particular, check with your doctor, health care provider or pharmacist before taking your medicine:
- serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in association with ivermectin treatment. Stop using ivermectin and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.
- if you have a weak immune system.
- if you are known to have an impaired barrier between your blood and your brain, caused by a dysfunction of a certain carrier protein (P-glycoprotein or P-gp).
- if you live or have spent time in parts of Africa where people get infected with a type of worm called "*Loa loa*" – also called "eye-worm".
- if you live or have spent time in African areas. The use of diethylcarbamazine citrate (DEC), if you are infected with "*Onchocerca volvulus*", may result in increased risk of side effects, which may sometimes be serious.
- if you are taking albendazole, since a slight to moderate elevation of the liver enzymes can occur temporarily (see section 4). If you are treated with Ivermectin/Albendazole orodispersible tablets individually (outside the framework of a mass drug administration) your liver function will be monitored by your doctor. If you are treated within the scope of a mass drug administration, tell your doctor, health care provider or pharmacist about any history of liver disease, alcohol consumption, or co-administration of medicinal products and directly report any clinical signs of hepatic adverse reactions (see section 4).
- if you already have reduced liver function the use of albendazole can temporarily lead to a reduction in the blood count (see section 4). If you are treated with Ivermectin/Albendazole orodispersible tablets individually (outside the framework of a mass drug administration) your blood counts will be monitored by your doctor.
- if you are elderly.
- in patients treated with albendazole, an already existing brain infection (neurocysticercosis) can be detected, especially in areas with pronounced tapeworm infection. Neurological symptoms may occur in these patients, such as seizures, increased cerebral pressure or specific neurological symptoms resulting from an inflammatory reaction caused by the death of the parasites in the brain. The symptoms may occur shortly after the treatment. Immediate treatment with corticosteroids and anti-convulsants (medicines used to treat seizures) should be initiated. If you are treated individually (outside the framework of a mass drug administration) your eyes will be checked before you are given with Ivermectin/Albendazole orodispersible tablets.

If any of the above apply to you (or you are not sure), talk to your doctor, health care provider or pharmacist before taking Ivermectin/Albendazole orodispersible tablets.

Children and adolescents
Ivermectin/Albendazole orodispersible tablets should not be used in children below the age of 5 years of age and weighing less than 15 kg, as the safety and efficacy have not been established in this patient groups.

Other medicines and Ivermectin/Albendazole orodispersible tablets
Tell your doctor, health care provider or pharmacist if you are taking, have recently taken or might take any other medicines.

Simultaneous intake of ivermectin and levamisole (used to treat parasitic worm infections) and clarithromycin (antibiotics used to treat bacterial infections), ketoconazole (medicines used to treat fungal infections), ciclosporin (used to treat autoimmune disease and preventing rejection of transplanted organs), verapamil and diltiazem (used to treat high blood pressure) may lead to increased blood levels of ivermectin. Simultaneous intake of ivermectin and alcohol and tranquiliser have the theoretical potential to increase ivermectins side effects.

It has been reported that cimetidine (used to treat stomach ulcers), praziquantel (used to treat parasitic infections) and dexamethazone (used to treat inflammation and allergy) when taken simultaneously increase the blood levels of the active metabolite of albendazole.

It has been reported that ritonavir (used to treat HIV infections), phenytoin, carbamazepine or phenobarbital (used to treat convulsions and epilepsy), and levamisole (used to treat parasitic worm infections), when taken simultaneously may reduce the blood levels of the active metabolite of albendazole. The importance for the course of the disease is not known, but it could lead to a decreased efficacy, especially in the treatment of systemic worm infestation diseases (helminthoses).

Ivermectin/Albendazole orodispersible tablets with drink
Simultaneous intake of orange juice may reduce your ivermectin blood levels whereas the simultaneous intake of grapefruit juice may increase your albendazole blood levels.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, health care provider or pharmacist for advice before taking this medicine.

Pregnancy

Mass drug administration campaign
The albendazole in this medicine can cause malformation to your unborn child. Therefore, you must not take Ivermectin/Albendazole orodispersible tablets within the framework of a mass drug administration if you are pregnant, think you may be pregnant or plan to have a baby (see section “Do not take Ivermectin/Albendazole orodispersible tablets”).

Pregnancy in women of childbearing age must be excluded before starting treatment with Ivermectin/Albendazole orodispersible tablets, by using a pregnancy test. Women of childbearing age are advised to take effective contraceptive measures shortly before, during treatment and within one month of termination of treatment regardless of whether treated in mass drug administration campaigns or in individual therapy.

Individual therapy (outside the scope of a mass drug administration)
If you are pregnant and you should be treated individually (outside the scope of a mass drug administration) with Ivermectin/Albendazole orodispersible tablets, this medicine should only be taken if clearly needed and if your doctor has instructed you to do so.

Breast-feeding

For the albendazole ingredient of Ivermectin/Albendazole orodispersible tablets, data on its use during breast-feeding in human and animals are not available. For the ivermectin ingredient of Ivermectin/Albendazole orodispersible tablets, it is known that it is excreted in human milk.

Individual therapy (outside the scope of a mass drug administration)
If you are taking Ivermectin/Albendazole orodispersible tablets for individual therapy (outside the scope of a mass drug administration) and want to breast-feed, talk to your doctor and only take Ivermectin/Albendazole orodispersible tablets if he/she has instructed you to do so.

Mass drug administration
If you are taking Ivermectin/Albendazole orodispersible tablets within the framework of a mass drug administration and plan to breast-feed, your doctor may decide to start your treatment one week after the birth of your child.

Driving and using machines
The effect of Ivermectin/Albendazole orodispersible tablets on the ability to drive and use machines has not been studied.
In some patients the possibility of side effects such as dizziness, drowsiness, or feeling shaky or like you are spinning, which may affect the ability to drive or use machines, cannot be ruled out. If you experience such symptoms, avoid driving or using machines.

Ivermectin/Albendazole orodispersible tablets contain sodium
This medicine contains less than 1 mmol sodium (23 mg) per orodispersible tablet, that is to say essentially 'sodium-free'.

3. How to take Ivermectin/Albendazole orodispersible tablets

Always take this medicine exactly as your doctor, health care provider or pharmacist has told you. Check with your doctor, health care provider or pharmacist if you are not sure.

The dose depends on your weight or height. Your doctor will tell you how many tablets you need to take. The recommended dose is:

Individual treatment (outside the framework of a mass drug administration)

Adults, adolescents and children aged 5 years and older with a body weight of:

Below 15 kg:	safety in patients with a body weight less than 15 kg body not been established
15 kg to less than 45 kg:	**one orodispersible tablet of 9 mg/400 mg** ivermectin/albendazole for **3 consecutive days**
45 kg and more:	**one orodispersible tablet of 18 mg/400 mg** ivermectin/albendazole for **3 consecutive days**

Alternatively, it is possible to choose your dose according to your height:

105 cm to 140 cm:	**one orodispersible tablet of 9 mg/400 mg** ivermectin/albendazole for **3 consecutive days**
141 cm and more:	**one orodispersible tablet of 18 mg/400 mg** ivermectin/albendazole for **3 consecutive days**

Mass drug administration

For mass drug administration, the recommended dose is:
- **one single oral dose of 9 mg/400 mg** ivermectin/albendazole orodispersible tablet **once a year** for patients weighing more than 15 kg but less than 45 kg, or with a height between 105 cm and 140 cm

- **one single oral dose of 18 mg/400 mg** ivermectin/albendazole orodispersible tablet **once a year** for patients weighing 45 kg or more, or with a height of more than 141 cm.

If required, the dose may be given **twice a year at 6-monthly intervals** in line with national treatment plans.

Use in children and adolescents
Use of Ivermectin/Albendazole orodispersible tablets in children below the age of 5 years is not recommended due to limited experience.
For all indications, the safety in children weighing less than 15 kg has not been established.

Elderly
Experience in older patients (≥65 years) is limited. Reports show that no dose adjustment is required. Ivermectin/Albendazole orodispersible tablets should however be used with caution in elderly patients, reflecting the greater frequency of concomitant disease or other medicine therapy.

How to take Ivermectin/Albendazole orodispersible tablets
Take Ivermectin/Albendazole orodispersible tablets by mouth. As the orodispersible tablet is fragile it should be removed from the blister with dry hands and taken immediately upon removing it from the blister. It should be placed on the tongue, where it will rapidly dissolve upon contact with saliva. It can be taken without water or can be dispersed in at least 20 mL of water and the resulting suspension completely taken. The dose should be taken with or after a meal.

Immediately upon opening the blister, remove the tablet and place the orodispersible tablet on the tongue.

If necessary, your doctor may also give you the Ivermectin/Albendazole orodispersible tablet dissolved in water through a feeding tube.

If you take more Ivermectin/Albendazole orodispersible tablets than you should
Contact your doctor, health care provider or pharmacist immediately.
In case of poisoning/overdosing, further treatment should be performed according to the clinical appearance or according to recommendations from information centres for poisoning cases.
As a result of poisoning, undesirable effects must be expected (see section 4). Therefore, controls of the blood count and the liver values are recommended in case of albendazole overdose. Decreased alertness including coma have been reported in patients with overdose of ivermectin.

If you forget to take Ivermectin/Albendazole orodispersible tablets
Take the dose as soon as possible and take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Ivermectin/Albendazole orodispersible tablets
Take Ivermectin/Albendazole orodispersible tablets as long as your doctor has advised you to. Do not stop your treatment as long as your doctor has not told you to, even if you feel better. If you do not finish your treatment completely, the infection can relaspse. It is important that you take all your Ivermectin/Albendazole orodispersible tablets treatment.

If you have any further questions on the use of this medicine, ask your doctor, health care provider or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequently reported side effect observed in the studies with Ivermectin/Albendazole orodispersible tablets was abdominal pain. Other side effects are listed below.

Stop using Ivermectin/Albendazole orodispersible tablets and seek medical attention immediately if you notice any of the following symptoms

- reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis).

Side effects to look out for and seek medical attention immediately

Allergic reactions

If you have an allergic reaction see a doctor straight away. The signs may include:

- sudden fever
- sudden skin reactions (such as rash or itching) or other serious skin reactions
- difficulty breathing.

Side effects seen in the study with Ivermectin/Albendazole orodispersible tablets or known for albendazole and ivermectin marketed as separate medicines

Very common side effects (may affect more than 1 in 10 people)

- headache
- abdominal pain
- increased liver enzymes

Common side effects (may affect up to 1 in 10 people)

- dizziness
- blurred vision
- changes to your vision (punctate opacity)
- cough
- diarrhoea, nausea, vomiting, inflammation of the gut induced by the parasite
- reversible hair loss
- acne
- fever

Uncommon side effects (may affect up to 1 in 100 people)

- decrease in the number of white blood cells (leukopenia)
- decrease in the amount of red blood cells or the red blood pigment haemoglobin (anaemia)
- allergic (hypersensitivity) reactions (including rash, itching and hives)
- feeling sleepy
- worsening or new onset of nerve disorders (fits, inflammation of the brain, paralysis of one body side, conspicuous tiredness)
- feeling faint (presyncope)
- inflammation of the eye called “pink eye” (conjunctivitis)
- bleeding in the whites of your eyes or swelling of your eye lids (limbitis)
- worsening of asthma
- abdominal bloating
- abdominal cramp
- constipation
- painful swallowing (odynophagia)
- passing gas
- indigestion (dyspepsia)
- inflammation of the mouth (stomatitis)
- inflammation of the liver (hepatitis)

- itching or rash
- joint pain
- nosebleeds
- decreased appetite
- increase in a certain enzyme in the blood (creatine phosphokinase)

Rare side effects (may affect up to 1 in 1 000 people)
- decreased amount of red blood cells (anaemia)
- abnormal brain function (encephalopathy, especially in *Loa loa* infection)
- bone pain
- protein in your urine

Very rare side effects (may affect up to 1 in 10 000 people)
- decrease in the number of all blood cells (pancytopenia)
- severely reduced blood cell counts (aplastic anaemia)
- severe decrease in the number of certain white blood cells (agranulocytosis)
- skin rash or skin reddening (erythema multiforme)

Not known (cannot be estimated from the available data)
- transient increase in certain white blood cells (eosinophilia)
- inflamed, enlarged or tender lymph nodes
- mental status changes
- depressed level of consciousness
- dizziness or a spinning sensation (vertigo)
- shaking (tremor)
- low blood pressure upon standing
- coma
- confusion
- unresponsiveness (stupor)
- lack of energy
- difficulty standing or walking
- pins and needles
- bleeding in the whites of your eyes (also known as red eye)
- abnormal sensation in the eyes
- eyelid swelling
- inflammation in the front part of the eye (anterior uveitis)
- inflammation of the clear outer layer of the eye (keratitis)
- inflammation of the back part of the eye affecting the retina and choroid (chorioretinitis) or inflammation of the blood vessel layer at the back of the eye (choroiditis)
- fast heart rate
- low blood pressure
- shortness of breath
- sore throat
- loss of control of your bowels
- loss of appetite
- upper abdominal pain
- increased blood bilirubin levels
- rash with hives
- skin inflammation upon contact
- muscle pain
- back or neck pain
- loss of control of your bladder
- blood in urine
- testicle pain and discomfort
- water retention (in arms, legs and face),
- extreme weakness, tiredness
- chills

- diffuse body pain
- increased sweating

The occurrence of the above mentioned undesirable effects differed depending on the treated parasite and the treatment duration (short-term or long-term).

Paediatric patients
You should observe your child for the above mentioned signs and symptoms, especially during the first 2 days and seek immediate medical care if your child shows any of the following symptoms: confusion, shaking, unusual sleepiness or agitation, swelling of the face or eyes, severe gut pain, persistent vomiting, or fever above 38°C that does not subside.

Reporting of side effects
If you get any side effects, talk to your doctor, health care provider or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ivermectin/Albendazole orodispersible tablets

Keep this medicine out of the sight and reach of children.

This medicinal product does not require any special storage conditions.

Do not use this medicine after the expiry date which is stated on the blister or carton after {EXP}. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ivermectin/Albendazole orodispersible tablets contain
- The active substances are ivermectin and albendazole.
  Ivermectin/Albendazole 9 mg/400 mg orodispersible tablets: each orodispersible tablet contains 9 mg ivermectin and 400 mg albendazole.
  Ivermectin/Albendazole 18 mg/400 mg orodispersible tablets: each orodispersible tablet contains 18 mg ivermectin and 400 mg albendazole.
- The other ingredients are: croscarmellose sodium (E468), povidone, mannitol (E421), butyl hydroxyanisole (E320), citric acid (E330), mango flavour *(consisting of flavouring preparations, flavouring substance, natural flavouring substance, maltodextrin, gum arabic (E414), triacetin (E1518), propylene glycol (E1520))*, sodium stearyl fumarate.

What Ivermectin/Albendazole orodispersible tablets look like and contents of the pack

Ivermectin/Albendazole 9 mg/400 mg orodispersible tablets
Round, white to almost white, orodispersible tablets of approximately 16 mm of diameter, debossed with “9/400” on one side.

Ivermectin/Albendazole 18 mg/400 mg orodispersible tablets
Round, white to almost white, orodispersible tablets of approximately 16 mm of diameter, debossed with “18/400” on one side.

Pack sizes
10, 30, 60 and 80 orodispersible tablets in blister with and without desiccant.

Not all pack sizes may be marketed.

Scientific Opinion Holder
Laboratorios Liconsa, S.A.
Calle Dulcinea S/N
Alcalá de Henares
28805 Madrid
Spain

Manufacturer
Laboratorios Liconsa, S.A
Avda. Miralcampo 7
Polígono Industrial Miralcampo
19200 Azuqueca de Henares
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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Indicated patient groups

Ivermectin/Albendazole 9 mg/400 mg orodispersible tablets

			
Height: 105 cm to 140 cm	Weight: 15 kg to less than 45 kg	Age: 5 years and older	Do not use for MDA during pregnancy or with the intention of becoming pregnant. (Use not recommended for individual therapy)

Ivermectin/Albendazole 18 mg/400 mg orodispersible tablets

			
Height: 141 cm and higher	Weight: 45 kg and more	Age: 5 years and older	Do not use for MDA during pregnancy or with the intention of becoming pregnant. (Use not

recommended for
individual therapy)