SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VERMOX 500 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains:
Active substance: mebendazole 500 mg
Excipients with known effects: lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hydatid disease (E. granulosus, E. multilocularis) when surgery is not an option.
Pre- and postoperative prophylaxis of hydatid disease treated with surgery, in order to prevent the risk of spread or in cases where a radical excision or a complete drainage of the hydatid cysts is not possible.
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

The daily dosage is about 50 to 60 mg/kg of body weight. This dosage must be divided into 2-3 daily doses, to be taken after meals, because fats promote absorption of the drug.

This dosage can be reached gradually during the course of the first weeks of treatment.
The drug must be administered with monitoring for the therapeutic effects at appropriate intervals (by means of ultrasound, radiography, CT, scintigraphy, depending on the site of the hydatid cysts).
Treatment periods can range from a minimum of 1 month (pre-operative prophylaxis) to several months: there are even reports in the literature of treatment periods of over 3 years.

The tablets can be swallowed with water and chewed or swallowed whole.

<u>VERMOX oral suspension should be considered for patients such as young children who are unable to swallow the tablet.</u>

If needed, the tablet must be crushed before it is given to a young child. A child must always be supervised while they are taking VERMOX.

Children under 2 years of age:
VERMOX has not been extensively studied in children below the age of 2 years.

Currently available data are described in section 4.4, 4.8 and 5.2, but no recommendations on a posology can be made.
Because of the lack of sufficient safety data, VERMOX should not be used in children below the age of 1 year (see section 4.4, 4.8 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
VERMOX 500 mg tablets is contraindicated in children under one year old for massive treatment of single or mixed gastrointestinal infestations.

4.4 Special warnings and precautions for use

Convulsions in children, including in infants below one year of age, have been reported very rarely during postmarketing experience with VERMOX (see section 4.8). VERMOX has not been extensively studied in children below the age of 2 years. Therefore, VERMOX should be used in children aged 1-2 years only if the potential benefit justifies the potential risk.
Because of the lack of sufficient safety data, VERMOX should not be used in children below the age of 1 year.

Glomerulonephritis and agranulocytosis have been reported very rarely with dosages substantially higher than those recommended and for prolonged periods of treatment.

Results from a case-control study investigating an acute case of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) suggested a possible relationship between SJS/TEN and the concomitant use of mebendazole and metronidazole. Further data on this type of interaction are not available. Therefore, concomitant use of mebendazole and metronidazole must be avoided.

As higher doses and longer treatment is recommended in patients with Echinococcosis, careful consideration should be given when treating patients with severe chronic hepatic diseases and/or bone marrow depression.
These patients should be closely monitored with hematological, liver and renal function tests. Consider discontinuing VERMOX if clinically significant laboratory abnormalities are found. Official guidelines should be taken into consideration.

Important information about some excipients
VERMOX 500 mg tablets contains lactose; patients suffering from rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption must not take this medicine.

VERMOX 500 mg tablets contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5. Interaction with other medicinal products and other forms of interaction

Concomitant treatment with cimetidine may inhibit the metabolism of mebendazole in the liver, resulting in increased plasma concentrations of the drug, especially during prolonged treatment. Concomitant use of mebendazole and metronidazole should be avoided (see section 4.4).

4.6 Pregnancy and lactation

Mebendazole has shown embryotoxic and teratogenic activity in rats and mice. No harmful effects on reproduction have been observed in other animal species tested.

The possible risks associated with prescribing VERMOX 500 mg in pregnancy, particularly during the first trimester, must be weighed against the expected therapeutic benefits.

Breastfeeding
Limited data from case reports show that a small amount of mebendazole is present in breast milk after oral administration. Therefore, caution should be exercised when VERMOX 500 mg is administered to breastfeeding women.

4.7 Effects on ability to drive and use machines

No studies have been conducted on the ability to drive and use machines.

4.8 Undesirable effects

In this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of VERMOX based on the comprehensive assessment of the available adverse event information. A causal relationship with VERMOX cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and cannot reflect the rates observed in clinical practice.

The safety of VERMOX was evaluated in 6276 subjects who participated in 39 clinical trials for treatment of single or mixed parasitic infestations of the gastrointestinal tract. In these 39 clinical trials, no adverse reactions (adverse drug reactions, ADRs) were reported in ≥1% of VERMOX-treated subjects. The ADRs reported in clinical trials and during postmarketing experience with VERMOX are shown in Table 1. Frequencies are stated according to 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 (the frequency cannot be defined on the basis of the available data).

Table 1: Adverse drug reactions identified during post marketing experience with VERMOX, reported by frequency category estimated from clinical studies.

Classification by systems and organs	**Adverse drug reactions**				
	Frequency				
	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),

Blood and lymphatic system disorders				Neutropenia	Agranulocitosis*
Immune system disorders				Hypersensitivity reactions such as anaphylactic and anaphylactoid reactions	
Nervous system disorders				Convulsions, vertigo	
Gastrointestinal disorders		Abdominal pain	Abdominal disorders, diarrhea, flatulence nausea, vomiting		
Hepatobiliary disorders				Hepatitis, abnormal liver function tests	
Skin and subcutaneous tissue disorders				Rash, toxic epidermal necrolysis, Stevens-Johnson syndrome, exanthema, angioedema, urticaria, alopecia	
Renal and urinary disorders					Glomerulonephritis*

***** Observe at higher and longer doses

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 at the address https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9 Overdose

In patients treated at dosages substantially higher than recommended or for prolonged periods of time, the following adverse reactions have been reported rarely: alopecia, reversible liver function disturbances, hepatitis, agranulocytosis, neutropenia, and glomerulonephritis. With the exception of agranulocytosis and glomerulonephritis, these adverse reactions have also been reported in patients who were treated at standard dosages (see section 4.8).

Signs and symptoms
In the event of accidental overdose, abdominal cramps, nausea, vomiting and diarrhea may occur.

Treatment
There is no specific antidote. Activated charcoal may be given if appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthelmintics for oral administration, benzimidazole derivatives.
ATC code: P02CA01

In therapeutic indications (see section 4.1), mebendazole acts locally in the lumen of the stomach by interfering with cellular tubulin formation in the intestines of parasites. Mebendazole binds specifically to tubulin and causes ultrastructural degenerative changes in the intestine. As a result of this process, glucose absorption by the parasites is blocked, and their digestive functions are disrupted, leading to an autolytic process.

5.2 Pharmacokinetic properties

Following oral administration mebendazole is scarcely absorbed. Most of the oral dose remains in the gastrointestinal tract.
In healthy volunteers, following oral administration of 1.5 g of mebendazole with a high fat meal, plasma concentrations were 17-134 nM/1; prolonged administration of 1 g of mebendazole led to an increase of 0-500 nM/1 in the plasma concentration. At therapeutic dosages bioavailability is low, because the drug is subject to an extensive first pass metabolism and because of its low solubility. About 90% of the absorbed portion is bound to plasma proteins.
In hepatic hydatid disease, following oral administration of 1 g of mebendazole, plasma peaks occurred between the 3rd and 6th hours (0.12-0.28 µg/mL): the distribution of mebendazole between blood and cyst liquid was 1:0.7.

Paediatric population
Limited data of the mebendazole concentrations in plasma are available in children and adolescents 1 to 16 years of age. These data do not indicate substantially higher systemic exposure to mebendazole in subjects 3 to 16 years of age compared to adults.
In subjects 1 to <3 years of age, systemic exposure is higher than in adults due to higher mg/kg dose relative to adults.

5.3 Preclinical safety data

- **Acute administration:**
  LD 50 (albino rat, oral route): 1500 mg/kg;
  LD 50 (albino mouse, oral route): 1500 mg/kg.

- **Prolonged administration:**
  Albino rat oral route (28 days): maximum dose not causing alterations: 200 mg/kg/day;
  Albino rat oral route (180 days): maximum dose not causing alterations: 40 mg/kg/day;
  Dog oral route (180 days): maximum dose not causing alterations: 40 mg/kg/day.

No suspected carcinogenic histological manifestations.

- **Fetal toxicity:**
  Albino female rat, oral route: increase in resorptions (30 mg/kg/day);
  Female rabbit, oral route: maximum dose not causing alterations 30 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

One tablet contains:
Excipients: **lactose monohydrate**; methylcellulose; sodium starch glycolate; microcrystalline cellulose; corn starch; magnesium stearate; anhydrous colloidal silica.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Thirty 500 mg tablets in opaque blisters

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

Janssen-Cilag SpA
Viale Fulvio Testi, 280/6
20126 Milano MI

8. MARKETING AUTHORIZATION NUMBER

Thirty 500 mg tablets MA n. 023821034

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: May 1985
Date of latest renewal: June 2005

10. DATE OF REVISION OF THE TEXT

November 2023