SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

ESTROMEB (Mebendazole Oral Suspension 100 mg/5 ml)

2. Qualitative and quantitative composition

Each 5 ml contains:
Mebendazole USP 100 mg
Flavoured Syrup Base q.s.
Colour: Carmoisine
For a full list of excipients, see section 6.1

3. Pharmaceutical form

Oral Suspension
A light pink coloured flavoured suspension.

4. Clinical particulars

4.1 Therapeutic indications

Broad spectrum gastrointestinal anthelmintic indicated for the treatment of:
Enterobius vermicularis (threadworm/pinworm)
Oxyuris vermicularis
Trichuris trichuria (whipworm)
Ascaris lumbricoides (large roundworm)
Ancylostoma duodenale (common hookworm)
Necator americanus (American hookworm)
There is no evidence that Estromeb is effective in the treatment of cysticercosis.

4.2 Posology and method of administration

Adults and children over 2 years:
Enterobiasis:
1 x 5 ml (1 dosing cup).
It is highly recommended that a second dose is taken after 2 weeks, if reinfection is suspected.
Ascariasis, trichuriasis, ancylostomiasis, necatoriasis and mixed infections:
1 x 5 ml (1 dosing cup) bd for three days.
Children under 2 years:
Estromeb 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, Estromeb should not be used in children below the age of 1 year (see section 4.4, 4.8 and 5.2).

Method of administration.
Oral Use
Estromeb oral suspension should be considered for patients such as young children who are unable to swallow the tablet.

4.3 Contraindications

Estromeb is contraindicated in pregnancy and in patients who have shown hypersensitivity to the product or any components.

4.4 Special warnings and precautions for use

Not recommended in the treatment of children under 2 years

There have been rare reports of reversible liver function disturbances, hepatitis and neutropenia described in patients who were treated with mebendazole at standard dosages for indicated conditions (see section 4.8 'Undesirable effects'). These events, along with glomerulonephritis and agranulocytosis, have also been reported with dosages substantially above those recommended and with treatment for prolonged periods of time.

A case-control study of a single outbreak of Stevens-Johnson syndrome /toxic epidermal necrolysis (SJS/TEN) suggested a possible association with the concomitant use of metronidazole with mebendazole. Although there are no additional data on this potential interaction, concomitant use of mebendazole and metronidazole should be avoided.

Convulsions in children, including in infants below 1 year of age, have been reported very rarely during post-marketing experience (see section 4.8 'Undesirable effects'). Estromeb has not been extensively studied in children below the age of 2 years. Therefore, Estromeb 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, Estromeb should not be used in children below the age of 1 year.

Estromeb should only be given to very young children if their worm infestation interferes significantly with their nutritional status and physical development.

Estromeb oral suspension contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicinal product contains less than 1 mmol sodium (23 mg) per mL, 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.
Concomitant use of mebendazole and metronidazole should be avoided (see section 4.4).

4.6 Fertility, pregnancy and lactaction

Pregnancy
Since Estromeb is contraindicated in pregnancy, patients who think they are or may be pregnant should not take this preparation.

Breast-feeding
Limited data from case reports demonstrate that a small amount of mebendazole is present in human milk following oral administration. Therefore, caution should be exercised when Estromeb is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines
Estromeb has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Throughout this section adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of Estromeb based on the comprehensive assessment of the available adverse event information. A causal relationship with Estromeb 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 may not reflect the rates observed in clinical practice.
The safety of Estromeb was evaluated in 6276 subjects who participated in 39 clinical trials for the treatment of single or mixed parasitic infestations of the gastrointestinal tract. In these 39 clinical trials, no adverse drug reactions (ADRs) occurred in ≥1% of Estromeb-treated subjects.
ADRs identified from clinical trials and post-marketing experience with Estromeb are included in Table 1. The displayed frequency categories use the following convention:
Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1000 to <1/100); Rare (≥1/10,000 to <1/1000); Very rare (<1/10,000), Not known (cannot be estimated from the available data).
Table 1: Adverse Drug Reactions Reported in Clinical Trials and Post-marketing Experience for Estromeb

System Organ Class	**Adverse Drug Reactions**		
	Frequency Category		
	Common (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1000 to < 1/100)	**Rare** (≥1/10,000 to <1/1000)
Blood and Lymphatic System Disorders			Neutropenia[b] Agranulocytosis[b] *
Immune System Disorders			Hypersensitivity including anaphylactic reaction and anaphylactoid reaction[b]
Nervous System Disorders			Convulsions[b] Dizziness[a]
Gastrointestinal Disorders	Abdominal pain[a]	Abdominal discomfort[a]; Diarrhoea[a]; Flatulence[a] Nausea[a], Vomiting[a]	
Hepatobiliary Disorders			Hepatitis; [b] Abnormal liver function tests[b]
Skin and Subcutaneous Tissue Disorders			Rash[a] Toxic epidermal necrolysis [b]; Stevens-Johnson syndrome [b]; Exanthema [b]; Angioedema [b]; Urticaria [b]; Alopecia [b]
Renal and Urinary Disorders			Glomerulonephritis[b] *

[a] ADR frequency data derived from Clinical Trials or Epidemiological Studies

[b] ADRs not observed in clinical trials and frequency calculated based on 6276 patients exposed in clinical trials and epidemiological studies, divided by 3 (Frequency = 1/2092).
* Observed in higher and prolonged doses

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

4.9 Overdose

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 also have been reported in patients who were treated with mebendazole at standard dosages (see section 4.8).

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

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anthelmintic for oral administration, benzimidazole derivatives;

ATC code: P02CA01.

In vitro and in vivo work suggests that mebendazole blocks the uptake of glucose by adult and larval forms of helminths, in a selective and irreversible manner. Inhibition of glucose uptake appears to lead to endogenous depletion of glycogen stores within the helminth. Lack of glycogen leads to decreased formation of ATP and ultrastructural changes in the cells.
There is no evidence that Estromeb is effective in the treatment of cysticercosis.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, < 10% of the dose reaches the systemic circulation, due to incomplete absorption and pre-systemic metabolism (first-pass effect). The majority of an orally administered dose remains in the gastrointestinal tract. Maximum plasma concentrations are generally seen 2 to 4 hours after administration. Administration with a high fat meal increases the bioavailability of mebendazole, but the overall effect of food on the amount of drug remaining in the gastrointestinal tract is not expected to be substantial.

Distribution

The plasma protein binding of mebendazole is 90 to 95%. The volume of distribution is 1 to 2 L/kg, indicating that mebendazole penetrates areas outside the vascular space. This is supported by data in patients on chronic mebendazole therapy (e.g., 40 mg/kg/day for 3-21 months) that show drug levels in tissue.

Metabolism
Orally administered mebendazole is extensively metabolised primarily by the liver. Plasma concentrations of its major metabolites (hydrolysed and reduced forms of mebendazole) are substantially higher than those of mebendazole. Impaired hepatic function, impaired metabolism, or impaired biliary elimination may lead to higher plasma levels of mebendazole.

Elimination
Mebendazole, the conjugated forms of mebendazole, and its metabolites likely undergo some degree of enterohepatic recirculation and are excreted in the urine and bile. The apparent elimination half-life after an oral dose ranges from 3 to 6 hours in most patients.

Steady-state pharmacokinetics
During chronic dosing (e.g., 40 mg/kg/day for 3-21 months), plasma concentrations of mebendazole and its major metabolites increase, resulting in approximately 3-fold higher exposure at steady-state compared to single dosing.

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

In animal reproduction studies, adverse developmental effects (i.e., skeletal malformations, soft tissue malformations, decreased pup weight, embryolethality) were observed when mebendazole was administered to pregnant rats and mice throughout the period of organogenesis or as a single oral dose as low as 10 mg/kg in rats (approximately 0.2-fold the maximum recommended human dose (MRHD)). Maternal toxicity was present at the highest of these doses. Dosing of hamsters and rabbits did not result in embryotoxicity or teratogenicity. Doses up to 40 mg/kg in rats (0.8-fold the MRHD, based on mg/m^2), given to males for 60 days and to females for 14 days prior to gestation, had no effect upon foetuses and offspring.

No mutagenic activity was observed with mebendazole in bacterial reverse mutation tests. Mebendazole was mutagenic when tested in the mouse lymphoma thymidine kinase assay and aneugenic in vitro in mammalian somatic cells. In the in vivo mouse micronucleus assay, orally administered mebendazole induced an increased frequency of micronucleated polychromatic erythrocytes with evidence suggestive of aneugenicity.

Mebendazole had no carcinogenic effects at doses as high as 40 mg/kg/day when administered daily in the diet over 2 years in carcinogenicity tests in mice and rats (0.4 to 0.8-fold the MRHD, based on mg/m^2).

6. Pharmaceutical particulars

6.1 List of excipients

Sr.No.	Raw Material	Pharmacopoeia
1.	Sucrose	BP
2.	Propylene Glycol	BP
3.	Methyl Hydroxybenzoate	BP
4.	Propyl Hydroxybenzoate	BP
5.	Sodium Benzoate	BP
6.	Polysorbate-80	BP
7.	Saccharin Sodium	BP
8.	Sodium Citrate	BP
9.	Carmellose Sodium	BP
10.	Glycerol	BP
11.	Sorbic Acid	BP
12.	Colour Carmoisine Supra	IHS
13.	Essence Vanilla	IHS
14.	Essence Rose White	IHS
15.	Sodium Hydroxide	BP
16.	Purified Water	BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30℃ in dark place. Do not freeze.

6.5 Nature and contents of container

30 ml filled in an amber coloured PET bottle packed in carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Kilitch Drugs (India) Limited
37, Ujagar Industrial Estate,
W.T Patil Marg, Deonar,
Mumbai 400 088,Maharashtra, India.
Website- www.kilitch.com

8. Marketing authorisation number(s) issued by Ethiopian FDA

08092/09195/NMR/2021

9. Date of first authorisation/renewal of the authorisation

12-11-2022

10. Date of revision of the text

06/07/2023