SUMMARY PRODUCT CHARACTERISTIC (SPC)

MEBENDAZOLE
TABLETS

1. NAME OF THE MEDICINAL PRODUCT
1.1 TRADE NAME – Mebendazole
1.2 INTERNATIONAL NON-PROPERTY NAME – Mebendazole

2. CUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredient: Mebendazole
Each 100 mg tablet contains 100 mg mebendazole.
Each 500 mg tablet contains 500 mg mebendazole.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Mebendazole 100 mg tablets are white or almost white, round, biconvex and scored in half on one side.
Mebendazole 5**00 mg tablets** are white with a yellowish tint, round, flat and with bevel edge of two sides.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Mebendazole 100 mg tablets:
For the treatment of patients 2 years of age and older of *Trichuris trichuria* (whipworm), *Enterobius vermicularis* (pinworm or threadworm), *Ascaris lumbricoides* (roundworm), *Ancylostoma duodenale* (common hookworm), *Necator americanus* (American hookworm) in single or mixed gastrointestinal infestations.
There is no evidence that Mebendazole 100 mg tablets are effective in the treatment of cysticercosis.
Mebendazole 500 mg tablets:
Mebendazole is an anthelmintic indicated for the treatment of patients 2 years of age and older with gastrointestinal infections caused by:
- *Ascaris lumbricoides* (roundworm)
- *Trichuris trichiura* (whipworm)

4.2 Posology and method of administration
Mebendazole 100 mg tablets:
Adults and children over 2 years:
For the control of trichuriasis, ascariasis and hookworm infections, one Mebendazole 100 mg tablet twice a day for three consecutive days.
For the control of enterobiasis a single tablet is administered. It is highly recommended that a second tablet is taken after two weeks, if reinfection is suspected.
Tablets may be chewed or swallowed whole. Crush the tablet before giving it to a young child. Always supervise a child while they are taking this medicine.
Mebendazole 500 mg tablets:
The recommended dosage in patients 2 years of age and older is one Mebendazole 500 mg tablet taken as a single dose.
Chew Mebendazole 500 mg tablet completely before swallowing. Do not swallow the tablet whole.

For patients who have difficulty chewing the tablet, Mebendazole 500 mg tablet can be placed in a spoon and approximately 2 mL to 3 mL of drinking water added onto the tablet using a dosing syringe. Within 2 minutes, the tablet absorbs the water and turns into a soft mass with semi-solid consistency, which can then be swallowed.

Method of Administration

Oral use. Mebendazole tablets can be taken without regard to food intake.

4.3 Contraindications

Mebendazole 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 (see *Pediatric Use*).

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.

Risk of Convulsions

Convulsions have been reported in infants below the age of 2 years during post-marketing experience with Mebendazole.

Hematologic Effects

Agranulocytosis and neutropenia have been reported with mebendazole use at higher doses and for more prolonged durations than is recommended for the treatment of soil-transmitted helminth infections. Monitor blood counts if Mebendazole is used at higher doses or for prolonged duration.

Pediatric Use

The safety and effectiveness of Mebendazole tablets have been established in pediatric patients 2 to 16 years of age. Use of Mebendazole tablets in children is supported by evidence from adequate and well-controlled studies of Mebendazole tablets.

The safety and effectiveness of mebendazole, including Mebendazole have not been established in pediatric patients less than 2 years of age. Convulsions have been reported with mebendazole use in this age group.

Geriatric Use

Clinical studies of mebendazole did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

Adult Use

The safety and effectiveness of Mebendazole tablets have been established in adults for the treatment of gastrointestinal infections by *T. trichiura* and *A. lumbricoides*. Use of Mebendazole mg tablets in adults for these indications is supported by evidence from an adequate and well-controlled trial in pediatric patients ages 2 to 16 years *[see Clinical Studies (14.1)]*, safety data in adults *[see Adverse Reactions (6.1)]*, pharmacokinetic data in adults *[see Clinical Pharmacology (12.3)]*, and the evidence from published literature.

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 lactation

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

Lactation

As it is not known whether mebendazole is excreted in human milk, it is not advisable to breast feed following administration of Mebendazole.

4.7 Effects on ability to drive and use machines

Mebendazole 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 Mebendazole based on the comprehensive assessment of the available adverse event information. A causal relationship with Mebendazole 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 Mebendazole 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 Mebendazole treated subjects.

ADRs identified from clinical trials and post-marketing experience with Mebendazole 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 Mebendazole

System Organ Class	Adverse Reaction	Frequency
Blood and lymphatic system disorders	Neutropenia[b]	Rare
	Agranulocytosis[b]	Rare
Immune system disorders	Hypersensitivity including anaphylactic reaction and anaphylactoid reaction[b]	Rare
Nervous system disorders	Convulsions[b]	Rare
	Dizziness[a]	Rare
Gastrointestinal disorders	Abdominal pain[a]	Common
	Abdominal discomfort[a]	Uncommon
	Diarrhoea[a]	Uncommon
	Flatulence[a]	Uncommon
Hepatobiliary disorders	Hepatitis[b]	Rare
	Abnormal liver function tests[b]	Rare
Skin and subcutaneous tissue disorders	Rash[a]	Rare
	Toxic epidermal necrolysis[b]	Rare
	StevensJohnson syndrome[b]	Rare
	Exanthema[b]	Rare
	Angioedema[b]	Rare

	Urticaria[b]	Rare
	Alopecia[b]	Rare
Renal and Urinary Disorders	Glomerulonephritis[a]	Not known

a - ADR frequency data derived from Clinical Trials or Epidemiological Studies.
b - ADRs not observed in clinical trials and frequency calculated using "Rule of 3", as detailed in SmPC guideline 2009. 6276 patients exposed in clinical trials and epidemiological studies, divided by 3 (Frequency = 1/2092). Note: frequencies differ from those reported in the August 2009 CCDS, as these were not calculated using the formula detailed in the SmPC guideline 2009.

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 Mebendazole 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 to extensive presystemic metabolism (first pass effect). Maximum plasma concentrations are generally seen 2 to 4 hours after administration. Dosing with a high fat meal leads to a modest increase in the bioavailability of mebendazole.

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 321 months) that show drug levels in tissue.

Metabolism

Orally administered mebendazole is extensively metabolised primarily by the liver. Plasma concentrations of its major metabolites (amino and hydroxylated amino 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 halflife after an oral dose ranges from 3 to 6 hours in most patients.

Steadystate pharmacokinetics

During chronic dosing (e.g., 40 mg/kg/day for 321 months), plasma concentrations of mebendazole and its major metabolites increase, resulting in approximately 3fold higher exposure at steadystate compared to single dosing.

5.3 Preclinical safety data

In carcinogenicity tests of mebendazole in mice and rats, no carcinogenic effects were seen at doses as high as 40 mg/kg (0.4 to 0.8-fold the MRHD, based on mg/m^2) given daily over two years. No mutagenic activity was observed with mebendazole in a bacterial reverse gene mutation test. Mebendazole was mutagenic in the absence of S-9 when tested using a continuous (24 hour) treatment incubation period in the mouse lymphoma thymidine kinase assay. Mebendazole was 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. 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 fetuses and offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each Mebendazole 100 mg tablet contains:
Microcrystalline cellulose
Maize starch
Sodium starch glycolate
Magnesium stearate
Talc purified
Sodium lauryl sulfate

Each Mebendazole 500 mg tablet contains:
Microcrystalline cellulose
Maize starch
Sodium starch glycolate
Magnesium stearate
Talc purified
Sodium lauryl sulfate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Storage conditions

Store at temperature not higher than 25^0C, out of the reach of children, in original pack.

6.5 Nature and contents of container

100 mg Mebendazole tablets: 1 blister packet with 10 tablets in each and leaflet inserted in the cardboard box.
500 mg Mebendazole tablets: 1 tablet in labeled plastic bottle with leaflet inserted in the cardboard box.

6.6 Special precautions for disposal and other handling

No special requirements

7. MANUFACTURER
"ARPIMED" LLC
Bldg. 19, mcr 2-nd, Abovyan, Kotayki Marz, Republic of Armenia
Tel.: (374) 222 21703 Fax: (374) 222 21924

8. MARKETING AUTHORIZATION HOLDER
"ARPIMED" LLC
Bldg. 19, mcr 2-nd, Abovyan, Kotayki Marz, Republic of Armenia
Tel.: (374) 222 21703 Fax: (374) 222 21924

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
100 mg Mebendazole tablets – 16.12.2002
500 mg Mebendazole tablets – 27.12.2002

10. DATE OF REVISION OF THE TEXT