SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zestaval 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains albendazole 200 mg.

Excipient(s) with known effect:
Each film-coated tablet contains 150 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, film-coated tablets with star embossed on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Zestaval is suitable for the treatment of the following helminthoses:

Cystic echinococcosis (*Echinococcus granulosus* infection, dog tapeworm infestation)
- inoperable progressive form
- non-radically operable progressive form
- pre-surgical support of the surgical therapy

Alveolar echinococcosis (*Echinococcus multilocularis* infection, fox tapeworm infestation)
- inoperable progressive form
- non-radically operable progressive form
- pre-surgical support of the surgical therapy

Trichinae infestation (*Trichinella spiralis* infection, trichinosis)

A treatment attempt for dwarf nematode infestation (*Strongyloidiasis, Strongyloides stercoralis*) is indicated.

4.2 Posology and method of administration

Posology

Cystic or alveolar echinococcosis

A treatment cycle consists of 2 tablets of 200 mg active ingredient twice a day for 28 days, followed by a 14-day break. At least two, but no more than three treatment cycles should follow each other.

- Pre-surgical:

If surgery treatment is planned, it should be preceded by treatment with Zestaval for 2 cycles as recommended above.

If surgery becomes necessary before two complete cycles are completed, Zestaval should be given for as long as possible, but for not longer than 28 days/cycle.

- Post-surgical:

If surgery is essential after less than 14 days of treatment, Zestaval should be administered after surgery for at least 2 treatment cycles of 28 days each with a 14-day break in between. 2 complete treatment cycles should also be given if cysts are still present after pre-surgical treatment or after cyst rupture.

People with a body weight of less than 60 kg should be treated with a daily dose of 15 mg active substance per kg body weight, divided into 2 single doses. The maximum dose is 800 mg/day.

Trichinosis
2 tablets of 200 mg active ingredient twice a day for 6 days.
Normally, one treatment cycle is necessary.

Confirmed diagnosis or suspected infestation of dwarf threadworms (strongyloidiasis)
2 tablets of 200 mg active ingredient once a day for 3 consecutive days.

Elderly people
Experience with elderly patients (65 years and older) is limited. Reports indicate that no dosage adjustment is necessary (see section 4.4).

Renal impairment
As the renal excretion of albendazole and its primary metabolite albendazole sulfoxide is negligible, the clearance of these components is unlikely to be altered in patients with renal impairment. An adjustment of the dosage is not required. Nevertheless, patients with evidence of renal insufficiency should be carefully observed.

Hepatic impairment
In patients with hepatic impairment, the warnings should be followed (see sections 4.4 and 4.8).

Method of administration

Oral use.

Zestaval should be taken in the morning and evening with meals, preferably with some liquid.

Note:
For better absorption of the active ingredient, a fat-containing diet is recommended for the time of treatment. This should be as solid as possible and certain over 40 g of fat per meal.

4.3 Contraindications

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

Albendazole should not be used during pregnancy or in women suspected of being pregnant. To exclude pregnancy, a test should be carried out in women of childbearing age before starting and regularly during treatment with albendazole (see section 4.6).

Albendazole treatment of children under 6 years of age is not recommended due to lack of therapeutic experience.

4.4 Special warnings and precautions for use

Since albendazole is rapidly degraded in the liver to its primary pharmacologically active metabolite, albendazole sulfoxide, it can be assumed that hepatic dysfunction has a significant effect on the pharmacokinetics of albendazole sulfoxide.

Slight to moderate elevations in liver enzymes may occur during treatment with albendazole, which usually return to normal after treatment discontinuation. Cases of hepatitis have also been reported.

Liver function tests should be performed before the start of each course of therapy, after 5 and 10 days, and at least every 2 weeks thereafter during therapy. If liver enzyme levels have increased significantly (more than twice the upper limits of the normal ranges), albendazole therapy should be discontinued. Re-treatment with albendazole can also be considered when levels return to normal, but patients should be monitored carefully and on more frequent (weekly) basis.

Patients who show abnormal values of liver function tests (transaminases) before starting treatment with albendazole should be carefully monitored and therapy should be discontinued if enzyme levels are significantly increased or blood cell counts drop to a clinically significant extent (see section 4.8).

Treatment with albendazole may lead to myelosuppression. Therefore, blood counts should be checked at the beginning of each treatment cycle, after 5 and 10 days and thereafter at 14-day intervals during each of the 28-day treatment cycles. Patients with liver disease, including hepatic echinococcosis, appear to be more susceptible to myelosuppression leading to pancytopenia, aplastic anaemia, agranulocytosis and leukopenia. In these patients, the blood count should therefore be monitored more closely. Albendazole should be discontinued if blood cell counts drop to a clinically significant extent (see section 4.8).

Albendazole should be used with caution in elderly patients and patients with renal impairment (see section 5.2).

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

In patients treated with albendazole, pre-existing neurocysticercosis may become apparent, especially in areas with marked taeniasis infection. These patients may experience neurological symptoms, such as seizures, increased intracranial pressure or focal symptoms, which are the result of an inflammatory reaction triggered by the parasites dying in the brain. Symptoms may appear shortly after treatment. Appropriate therapy with corticosteroids and anticonvulsants should be started immediately.

Zestaval contains lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Zestaval 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

The simultaneous administration of albendazole with cimetidine, praziquantel or dexamethasone increases the concentration of the active metabolite of albendazole in plasma.

Ritonavir, phenytoin, carbamazepine and phenobarbital may possibly decrease the plasma concentrations of the active metabolite of albendazole, albendazole sulfoxide. The clinical relevance of this is not known, but there could be reduced efficacy, especially in the treatment of systemic helminthosis. Patients should be monitored for efficacy and may require alternative dosing regimens or therapies.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no suitable data from the use of albendazole in pregnant women.
Data from animal studies have shown reproductive toxicity (see section 5.3). The possible risk to humans is not known. Albendazole should not be taken during pregnancy unless clearly necessary.
To exclude pregnancy, a test should be carried out in women of childbearing age before starting and regularly during treatment with Zestaval.
Because of the teratogenic properties of the benzimidazole derivatives, it is recommended to ensure that patients of childbearing potential use effective contraceptive measures. Due to unclear interactions with hormonal ovulation inhibitors, taking the "pill" alone is unsuitable for this purpose. Contraception must be used shortly before, during and for one month after Zestaval treatment.

Breast-feeding
Zestaval should not be used during breast-feeding as there are insufficient data in breast-feeding women or from animal studies.

Fertility
No data are available on the effect of albendazole on human fertility.

4.7 Effects on ability to drive and use machines

There are no indications so far that the ability to actively participate in road traffic or to operate machines is restricted.

4.8 Undesirable effects

Adverse reactions are listed below by system organ class and absolute frequency (all reported events). Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1.000 to < 1/100), rare (≥ 1/10.000 to <1/1.000), very rare (<1/10.000), not known (frequency cannot be estimated from the available data).

Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders*					
		Leukopenia		Pancytopenia, aplastic	

				anaemia, agranulocytosis	
Immune system disorders					
		Hypersensitivity reactions including skin rash, itching and urticaria.			
Nervous system disorders					
Headache	Dizziness	During the treatment of neurocysticercosis, existing symptoms worsened or new neurological disorders appeared (epilepsy, meningitis, hemiplegia, noticeable fatigue).			
Gastrointestinal disorders					
	Gastrointestinal complaints (abdominal pain, diarrhoea, nausea, vomiting). Gastrointestinal complaints have been associated with albendazole treatment in patients with echinococcosis.				
Hepatobiliary disorders					
Slightly to moderately elevated liver enzyme levels		Hepatitis. Results deviating from the norm in the liver biopsies have also been reported. However, these were probably a consequence of the worm infestation.			
Skin and subcutaneous tissue disorders					
	Reversible hair loss (thinning of the hair, moderate hair loss).			Erythema multiforme, Steven-Johnson syndrome.	
General disorders and administration site conditions					
	Fever	Nosebleed			

* Patients with liver disease, including hepatic echinococcosis, appear to be more susceptible to a myelosuppressive effect (see sections 4.2 and 4.4).

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 reaction via the national reporting system.

4.9 Overdose

Albendazole has only a low acute toxicity. So far, there have been no reports of intoxications.
Specific antidotes are not known.
Further treatment should be given according to clinical presentation or as recommended by poisoning information centres.

As increased attention must be paid to possible adverse effects after intoxication, checks of the blood count and liver enzymes are recommended (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthelmintics, Antinematodal agents, ATC code: P02CA03

Mechanism of action
Albendazole is a benzimidazole derivative with antiprotozoal and anthelmintic activity against intestinal and tissue parasites. Albendazole has larvicidal, ovicidal and vermicidal activity, which is thought to result from inhibition of polymerisation of the tubulin of the cytoplasmic microtubule system of intestinal parasites. This leads to the disruption of helminth metabolism, including a loss of energy, resulting in immobilisation of the susceptible helminths.
These pathophysiological changes lead to the death of the parasites.

5.2 Pharmacokinetic properties

Albendazole is lipophilic and is therefore poorly absorbed after oral administration (< 5%). Albendazole is subject to a high first-pass effect in the liver and is normally undetectable in plasma. It is rapidly metabolised to the main metabolite albendazole sulfoxide which is responsible for the anthelmintic effect. When albendazole is administered with a high-fat diet, the systemic exposure increases approximately five-fold. Emulsified fat (e.g. in liquid food), on the other hand, has no improving effect on availability. After oral administration of 400 mg albendazole with a breakfast (fat content about 40 g), the maximum plasma concentration of albendazole sulfoxide ranged from 1.8 to 6.2 µmol/l.

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

Elderly people
Although no studies have examined the effect of age on the pharmacokinetics of albendazole sulfoxide, data from 26 patients with echinococcal cysts suggest that the pharmacokinetics in these patients (aged up to 79 years) are similar to those in young healthy people. The number of elderly patients treated for echinococcosis or neurocysticercosis is limited. However, no problems were observed due to the increased age of the patients.

Renal impairment
The pharmacokinetics of albendazole have not been studied in patients with renal impairment.

Hepatic impairment
The pharmacokinetics of albendazole have not been studied in patients with liver dysfunction.

Albendazole sulfoxide was found in the cyst fluid at a level of about 15 to 20 % of the albendazole sulfoxide concentration in the blood plasma. Albendazole sulfoxide and its metabolites are excreted mainly in the bile and only to a small extent in the urine.
Elimination from cysts is significantly slower compared to elimination from plasma.
It can take several weeks after high and prolonged dosing.

5.3 Preclinical safety data

Acute toxicity
Albendazole has a low acute toxicity. The LD50 after oral administration ranged from 500 mg/kg to > 10,000 mg/kg body weight in mice, rats, rabbits and hamsters; only in pigs was the LD50 lower at 106 mg/kg body weight. Symptoms observed included weight loss, clonic convulsion, respiratory distress and diarrhoea.

Toxicity after repeated use
Studies up to 6 months in mice, rats and dogs suggested the target organs of toxicity to be the haematopoietic system and the liver. Regular monitoring of blood and liver values is therefore recommended for long-term therapy.

Reproductive toxicology
The teratogenicity of anthelmintically active benzimidazole derivatives is known.
In some animal models, albendazole is already teratogenic at doses that correspond to or come close to the human therapeutic dose. An influence on fertility was not observed.

Mutagenic and carcinogenic potential
Albendazole has not yet been subjected to extensive mutagenicity testing. However, albendazole showed no mutagenic properties in a series of *in vitro* tests (*S. typhimurium* reverse mutation test with or without metabolic activation, chromosome aberration test on CHO cells) and in a micronucleus test *in vivo* in the rat.

A cell transformation test on BALB/3T3 cells *in vitro* was weakly positive only after prior metabolic activation - carcinogenicity studies in rats and mice, however, gave no indication of a possible carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Lactose
Maize starch
Povidone
Microcrystalline cellulose
Sodium starch glycollate
Colloidal silicon dioxide
Magnesium stearate
Talc

Coating
Hypromellose

Polyethylene glycol 400
Titanium dioxide E171
Talc

6.2 Incompatibilities

None.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25 °C. Protect from light and moisture.

6.5 Nature and contents of container

Cardboard box containing Aluminium-PVC blister, of 2 film-coated tablets.
Pack size of 2 film-coated tablets.

6.6 Special precautions for disposal and other handling

No special precautions.

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd
Aharnon Str., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

N 17709

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 17 May 2013
Date of latest renewal: 19 June 2018

10. DATE OF REVISION OF THE TEXT

20/07/2023

For internal use only: am-spc-zestaval-200mg-fc-tabs-v01-r00-a0