1. NAME OF THE MEDICINAL PRODUCT

VERZOL® 400 mg tablet
VERZOL® oral suspension 40 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablet
Each tablet contains albendazole 400 mg.

Oral suspension
10 ml of suspension contain albendazole 400 mg.

Excipients with known effect:
Tablet: 200 mg lactose, 0.1 mg sodium methyl parahydroxybenzoate (E219), less than 0.01 mg sodium propyl parahydroxybenzoate (E217), 0.15 mg sunset yellow coloring (E110)

Oral suspension: 4.0 g of sucrose; 3.60 mg of orange-yellow dye S (E110); 20 mg sodium methyl parahydroxybenzoate (E219); 5.0 mg of sodium propyl parahydroxybenzoate (E217); 20.0 mg sodium benzoate (E211)

Excipients:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Light orange coloured, elongated, biconvex scored in one side tablet.
Oral suspension
Orange coloured suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intestinal and skin infections

- Threadworms (*Enterobius vermicularis*),
- Roundworms (*Ascaris lumbricoïdes*),
- Hookworms (*Ankylostoma duodenale*, *Necator americanus*),
- Whipworms (*Trichuris trichuria*),
- Anguillulosis (*Strongyloides stercoralis*),
- Taeniasis (*Taenia saginata*, *Taenia solium*),
- Giardiasis (*Gardia intestinalis* or *duodenalis*) in children,

Systemic infections

- Trichinosis (*Trichinella spiralis*).

4.2 Posology and method of administration

Posology

Indications	Daily dose	Treatment duration
Intestinal and skin infections (short-term treatment with lower dose)		
Oxyurosis	Children from 1 to 2 years: 5 ml suspension (200 mg) in one single dose Adults and children older than 2 years: 400 mg, 1 single tablet or 10 ml of suspension in single dose Strict hygiene measures should be taken and family environment should also be treated.	Single dose to be repeated 7 days after.
Roundworms Hookworms Whipworms	Children from 1 to 2 years: 5 ml of suspension (200 mg) Adults and children older than 2 years: 400 mg, 1 single tablet or 10 ml of suspension in single dose.	Single dose. *
Anguillulosis Taeniasis (associated with others parasitosis)	Adults and children older than 2 years: 400 mg, 1 tablet or 10 ml of suspension daily	1 daily dose during 3 days. *
Giardiasis	Children older than 2 years: 1 tablet or 10 ml of suspension daily.	1 daily dose during 5 days.
Systemic infections (long-term treatment with higher doses)		
Trichinosis	Children: 15 mg/kg/day divided into two daily doses without exceeding 800 mg/day Adults: 1 tablet of 400 mg or 10 ml of suspension twice daily	2 daily doses (morning & evening) during 10 to 15 days depending on the severity of the symptoms and on the onset of treatment.

* Particularly in case of anguillulosis, whipworm infection, taeniasis, if the worm control performed 3 weeks after the treatment is positive, a second treatment should be administered.
In case of intestinal and skin infections, you must talk to your doctor if you do not feel better or if you feel worse after 3 weeks.
For children under 6 years, tablet form of 400 mg is inappropriate due to wrong route risk, and only suspension form should be used.

Special populations
Elderly people:
Data concerning patients from 65 years old are limited. Reports suggest that no adaptation of the posology is required in elderly people. However, albendazole should be used with care in patients with a liver dysfunction.

Liver failure:
Albendazole is rapidly metabolized by the liver, the main metabolite, albendazole sulfoxide, is pharmacologically active. Hence, liver failure might result in significant effect on the pharmacokinetics of albendazole sulfoxide.
Patients with abnormal liver function tests (transaminases) prior to treatment with albendazole should be closely monitored. The treatment should be stopped in case of significant increase in liver enzymes or in case of clinically significant decrease in blood formula numeration (see section 4.4).

Renal failure:
As the elimination of albendazole and its main metabolite, albendazole sulfoxide are negligible, it is unlikely that the clearance of these compounds are modified in patients with renal failure. No dose adaptation of posology is required, however, patients with renal failure should be closely monitored.

Method of administration
Oral administration.
Neither purge, nor fast prior treatment is necessary.
In the treatment of trichinellosis, albendazole should be administered with meals.
Some people, notably young children and elderly people might have difficulties swallowing the full tablets. In this case it is advisable to chew the tablet with a little water or to crush it using VERZOL oral suspension can also be used.

4.3 Contraindications

- Hypersensitivity known to albendazole or to any of the excipients listed in section 6.1
- Pregnancy and women of childbearing age who do not use an efficient contraceptive method (see section 4.6)
- Breastfeeding

4.4 Special warnings and precautions for use

Neurologic symptoms
A treatment with albendazole might reveal a pre-existing neurocysticercosis, in particular in regions of strong infestation with taeniasis. Patients might feel neurological symptoms such as convulsions, increase in intracranial pressure and focal signs resulting from the inflammatory reactions following the death of the parasite in the brain. Symptoms might appear shortly after the treatment; an adapted treatment with corticoids and anticonvulsants should be immediately started.

Precaution for use when using albendazole for systemic infections (long-term treatment with higher doses):

- **Liver disorders**

Albendazole might result in a slight to moderate increase in liver transaminases, normalising generally when stopping the treatment. Serious cases of hepatitis have also been reported when treating systemic helminth infections (long-term treatment with higher doses) (see section 4.8). Tests of the liver function should be carried out prior to starting the treatment and at least every second week during the treatment. Albendazole shall be stopped in case of increase in hepatic enzymes (more than twice normal). If reintroducing the treatment is indispensable, this should be done after normalisation of liver enzymes. Moreover, a close monitoring should be carried out, keeping in mind that potential relapses might appear because an allergic mechanism cannot be discarded.

- **Medullar depression**

Cases of medullar depression have been reported during treatment of systemic helminth infections (long-term treatment with higher doses) (see section 4.8). Numerations of blood formula should be performed when starting the treatment and then every two weeks of treatment with albendazole during each 28-days cycle.
Patients with a liver disease, including liver echinococcosis, seem more likely to develop a medullar depression, leading to pancytopenia, medullar aplasia, agranulocytosis and leucopoenia. Then, an increase monitoring of the blood formula is recommended in patients showing a liver disease.
Albendazole shall be stopped in case of significant decrease in the number of blood cells (see section 4.2 and 4.8).
In the treatment of trichinosis, few data are available with albendazole in children under 6 years of age.
In the treatment of trichinosis, because of the activity, in particular on the intestinal forms and of the larvae in the early phase of the tissue migration, it is recommended to administer albendazole as early as possible at

the start of the infestation in order to decrease the symptoms and the complications. This treatment remains inactive on the encysted larvae in chronic forms and when it is initiated belatedly.

- Contraception

Before initiating the treatment with albendazole, the doctor should inform the patient of the embryotoxic, teratogenic and aneugenic risks of albendazole, of the necessity of an efficient contraception and of the potential consequences on pregnancy if it occurs during the course of the treatment with albendazole (see section 4.6).

Excipients with known effect:

Tablet and oral suspension:

These medicines contain sodium methyl parahydroxybenzoate (E219) and sodium propyl parahydroxybenzoate (E217). They can cause allergic reactions (possibly delayed). This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, i.e. essentially 'sodium free'.

Tablet:

This medicine contains lactose. Patients with galactose intolerance, total lactase deficiency or glucose or galactose malabsorption syndrome (rare hereditary diseases) should not take this medicine. This medicinal product contains an azo coloring agent (E110 Sunset yellow S) and may cause allergic reactions.

Oral suspension:

This medicinal product contains 4.0 g of sucrose. Patients with fructose intolerance, glucose-galactose malabsorption syndrome or sucrase/isomaltase deficiency (rare hereditary diseases) should not take this medicine. This medicinal product contains 20.0 mg sodium benzoate (E211) per 10 ml of suspension. It can lead to an increase in bilirubinemia following its displacement thanks to albumin, it can increase the risk of neonatal jaundice which can turn into kernicterus (deposition of unconjugated bilirubin in the brain tissue).

4.5 Interaction with other medicinal products and other forms of interaction

Precaution for use:

+ ritonavir

+ enzyme-inducing anticonvulsants

+ rifampicin

Significant decrease in plasma concentrations of albendazole and its active metabolite by the inducer, with risk of reduced efficacy.

Clinical monitoring of the therapeutic response and possible adjustment of the dosage of albendazole during treatment with the enzyme inducer and after its discontinuation.

4.6 Fertility, pregnancy and lactation

Female patients

Given the aneugenic, embryotoxic and teratogenic potential of albendazole, all the precautions should be taken in order to avoid pregnancy in these female patients. Treatment with albendazole should not be initiated before a negative result to a pregnancy test performed right before the treatment initiation. Women of childbearing age should use an efficient contraceptive method during the treatment and 6 months after stopping the treatment.

Male patients and their female partners

All precaution should be taken in order to avoid pregnancy in the partners of male patients treated with albendazole. It is not known if the presence of albendazole in sperm can cause teratogenic or genotoxic effects on human embryo/foetus. Men or their female partners of childbearing age must be informed of the obligation to use an efficient contraceptive method during all the course of the treatment with albendazole and during 3 months after stopping the treatment. Men whose partners are pregnant should be informed of the obligation to use a condom in order to reduce the exposition of their partner to albendazole.

Pregnancy
Studies in animal showed teratogenic embryotoxic effects in rat and rabbit at doses close to those used in men (see section 5.3). in clinical trials, the data on the use of albendazole during the first term of pregnancy are limited. Albendazole is contraindicated during pregnancy (see section 4.3 and 4.4), espacially because there are therapeutical alternatives that are better assessed in terms of safety in pregnant woman. Female patients should be informed of the necessity to consult their doctor immediately in case of pregnancy. This is based on prenatal monitoring targeted on malformations described in animal (skeletic, cranofacial, limbs).

Breasfeeding
Albendazole is present in human breast milk after a single dose of 400 mg. Because of its aneugenic activity, a risk for the new born child cannot be excluded. In case of a single dose, breastfeeding should be stopped at the time of intake and for at least 5.5 half-lives (about 48 hours) after stopping the treatment. Before initiating breastfeeding, pump all the available breask milk and dispose of it; in case of repeated intakes, breastfeeding is contraindicated.

Fertility
In rat or mouse, studies have showed testicular toxicity of albendazole (see section 5.3). albendazole has an aneugic activity, which is a risk factor for alteration of fertility in man.

4.7 Effects on ability to drive and use machines

No studies have been performed to evaluate the effect of albendazole on the ability to drive or use machines. when driving or using machines, it should be kept in mind that dizziness have been reported after using albendazole (see section 4.8).

4.8 Undesirable effects

The frequency of side effects very common to rare have been determined based on the data from the clinical trials. The frequencies of the other side effects are mainly based on the post-marketing data and are referred to the reported observations rather than the real frequencies.
The side effects listed below are classified by organ system and frequency, according to the following convention:
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
Unknown frequency (cannot be estimated based on the available data).

Intestinal and skin infections (short-term treatment with low doses)

Systemic class organs	Uncommon	Unknown frequency
Immune system disorders		Hypersensitivity reaction, including skin rash, itching and hives
Nervous system disorders	Headaches Dizziness (see section 4.7)	
Gastro-intestinal disorders	Gastro-intestinal symptoms (epigastric or abdominal pains, nausea, vomiting) and diarrhoea	
Hepatobiliary disorders		Increase in liver enzymes (see section 4.4)
Skin and subcutaneous tissue disorders		Polymorphic erythema Stevens-Johnson syndrome

Systemic infections (long-term treatment with higher doses)

Systemic class organs	Very common	Common	Uncommon	Unknown frequency
Haematological and lymph system disorders				*Medullar aplasia Leucopoenia Pancytopenia Agranulocytosis (see section 4.4)*
Immune system disorders			*Hypersensitivity reactions including skin rash, itching, hives*	
Nervous system disorders	*Headaches*	*Dizziness (see section 4.7)*		
Gastro-intestinal disorders		*Gastro-intestinal disorders (abdominal pains, nausea and vomiting)*		
Hepatobiliary disorders	*Slight to moderate increase in liver enzymes (see section 4.4)*		*Hepatitis (see section 4.4)*	
Skin and subcutaneous tissue disorders		*Reversible alopecia (decrease in thickness of the hair, moderate hair loss)*		*Polymorphic erythema, Stevens-Johnson Syndrome*
General disorders and administration site conditions		*Fever*		

Risk of allergic reactions due to the presence of yellow sunset E110 colouring agent.

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.

4.9 Overdose

In case of overdose, symptomatic treatment and medical monitoring are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiparasitics - antihelmintics, ATC code: P02CA03.

Albendazole is a benzimidazole carbamate. Albendazole is broad-spectrum antihelmintics, which is effective against a wide range of intestinal helminths.
Albendazole acts on helminths'cytoskeleton by the inhibition of tubulin polymerisation and thus, their introduction in the microtubules, blocking glucose absorption of parasites and resulting in their death.

Albendazole is also active on *Giardia intestinalis* (or *duodenalis*). It has an irreversible action that is targeted on the ventral disc of the trophozoites by acting on the polymerisation of tubulin and giardine, leading to a disorganisation of the cytoskeleton and micro strips. The ability of adhesion to the enterocytes is decreased, resulting in an inhibition of the growth and multiplication of the parasite.

5.2 Pharmacokinetic properties

Absorption and biotransformation
Following the administration, the low proportion of albendazole is absorbed (< 5 %) is metabolised into albendazole sulfoxide and sulfone. The plasma concentration in sulfoxide, the main active circulating metabolite reaches its maximum about two and a half hours after its administration.
The systemic pharmacological effect of albendazole is increased if the dose is administered concomitantly with a fat-rich meal, improving absorption by about 5.

Elimination
The plasma half-life of albendazole sulfoxide is 8 and a half hours.
Albendazole sulfoxide and its metabolites seem to be mainly eliminated by biliary route and for a lower proportion by urinary route.

Specific population
Renal failure: albendazole pharmacokinetics has not been studied in patients with renal failure.
Hepatic failure: albendazole pharmacokinetics has not been studied in patients with hepatic failure.

5.3 Preclinical safety data

Degeneration of the seminiferous tubules has been reported in cancerogenesis studies at dose of 100 mg/kg/day in mouse and 20 mg/kg/day in rat. A decrease in the testicle weight has been observed in dog treated with 60 mg/kg/day during 6 months. These doses correspond respectively to 2.4; 0.24 and 2.5 times the maximum therapeutic dose (based on the human equivalence). Albendazole has not altered fertility in males or female rat up to the maximum dose of 30 mg/kg/day, or 0.36 times the maximum therapeutic dose (based on the human equivalence).
Albendazole appeared to be teratogenic and embryotoxic in rat and rabbit.
Teratogenic effects were reported at doses greater than or equal to 6.6 mg/kg/day in rats and 30 mg/kg/day in rabbits. In a 3-generation reproduction study in rats, decreases in postnatal survival and growth were reported at 11.6 mg/kg/day. These doses correspond respectively to 0.1, 0.7 and 0.14 times the maximum therapeutic dose (based on a human equivalent dose).
No cancerogenic potential has been shown during the cancerogenesis studies in rats (20 mg/kg/day) and in mice (400 mg/kg/day). Albendazole did show any genotoxic effects in *in vitro* trials carried out on bacteria and mammal cells cultures, as well as in an *in vivo* micronucleus trial in rodents. A positive result has been reported in another micronucleus study in omuse and is regarded as resulting from an aneugenic effect of albendazole.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets:
Maize starch, lactose, sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), magnesium stearate, purified talc, colloidal anhydrous silica, sunset yellow supra colour (E110).

Suspension:
Saccharose, sorbitol, sodium carboxymethyl cellulose, sunset yellow supra colour (E110), orange flavour, banana flavourant, glycerine, sodium methyl parahydroxybenzoate (E219), sodium propyl

parahydroxybenzoate (E217), sodium benzoate (E211), sodium saccharin, citric acid, Tween 80, purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Keep out of sight and reach of children.
Protect from heat, light and moisture, store at a temperature not exceeding 30 °C.

6.5 Nature and contents of container

Tablet
Box of 1 tablet in blister pack (PVC-aluminium).

Suspension
Brown-glass bottle of 10 ml suspension.
Box of 20 sticks made of polyethylene terephthalate-aluminium-polyethylene terephthalate-polyethylene of 10 ml.

All pharmaceutical forms might not be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Exphar s.a. Zoning Industriel de Nivelles Sud, zone II
Av. Thomas Edison 105
1402 Thines (Belgium)

8. CATEGORY OF DISTRIBUTION

☐ Over-the counter medicine ☒ Prescription only medicines

List II

9. MANUFACTURER

Gracure Pharmaceuticals Ltd.
E-1105, Industrial Area, Phase-III
Bhiwadi, District Alwar (Raj.) INDIA

10. DATE OF REVISION OF THE TEXT

04/2022