Proposed professional information for VERMOX® 500 mg

SCHEDULING STATUS

S1

1. NAME OF THE MEDICINE

VERMOX® 500 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg mebendazole.

Excipients with known effect:

Contains sugar (34 mg lactose monohydrate per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

A white to faintly cream-coloured, bevel-edged tablet with "Me" 500 inscription on the one side and "JANSSEN" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VERMOX® 500 mg is indicated for the treatment of single and mixed helminth gastrointestinal infestations caused by:

- **Nematodes such as:**
- *Trichuris trichiura* (whipworm)

- *Ancylostoma duodenale* (hookworm)
- *Necator americanus* (hookworm)
- *Ascaris lumbricoides* (large roundworm)
- *Enterobius vermicularis* (pinworm)

4.2 Posology and method of administration

Whipworm; Hookworm; Large Roundworm; Pinworm: Adults and children older than 1 year: One tablet (500 mg) given as a single dose. The tablets may be crushed and given with some liquid for children.

A single dose of VERMOX® 500 mg may not be sufficient to cure infestations with hookworm and whipworm (Trichuris) although a substantial reduction in egg count can be expected.

A second course of treatment should be given to those patients who are still infected three to four weeks after the first course.

In worm-eradication campaigns the standard course should be administered every quarter during the first year.

The efficacy of VERMOX® is dependent upon the duration of physical contact between drug and parasite.

For infants under 1 year of age, see section 4.3 and 4.4.

4.3 Contraindications

VERMOX® 500 mg should not be used in children below the age of 1 years.

VERMOX® 500 mg is contraindicated in persons with a known hypersensitivity to mebendazole or to any of the other ingredients in VERMOX® 500 mg (see section 6.1).

VERMOX® 500 mg should not be given during pregnancy, as it is teratogenic in animals (see section 4.6).

Concomitant use of VERMOX® 500 mg and metronidazole should be avoided (see section 4.4 and 4.5).

4.4 Special warnings and precautions for use

Convulsions in children, including in infants below one year of age, have been reported during post-marketing experience with VERMOX® 500 mg (see section 4.8). VERMOX® 500 mg should not be given to children below 1 year of age. VERMOX® 500 mg or VERMOX® SD should not be used and VERMOX® 100 mg Tablets or VERMOX® 20 mg/mL should only be given to very young children if their worm infections interfere significantly with the nutritional status and the physical development.

To reduce the risk of choking, mebendazole oral suspension should be considered for patients such as young children who are unable to swallow the tablet.

There have been reports of reversible liver function disturbances, hepatitis, neutropenia, agranulocytosis and glomerulonephritis described in patients who were treated with dosages substantially above those recommended for prolonged periods of time (see section 4.9).

Results from a case control study investigating an outbreak of Stevens Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) indicated a possible relationship between SJS/TEN and the

concomitant use of VERMOX® 500 mg and metronidazole. Further data on interactions are not available. Therefore, concomitant use of VERMOX® 500 mg and metronidazole should be avoided (see section 4.3 and 4.5).

Patients with high parasitic burdens when treated with VERMOX® 500 mg have manifested diarrhoea and abdominal pain.

Lactose monohydrate

VERMOX® 500 mg contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency, or glucose-galactose malabsorption should not take VERMOX® 500 mg.

4.5 Interaction with other medicines and other forms of interaction

Concomitant treatment with cimetidine may inhibit the metabolism of the mebendazole in the liver, resulting in increased plasma concentrations of VERMOX® 500 mg especially during prolonged treatment.

Concomitant use of VERMOX® 500 mg and metronidazole should be avoided (see section 4.3 and 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

VERMOX® 500 mg is contraindicated during pregnancy (see section 4.3). Mebendazole has shown embryotoxic and teratogenic activity in rats and in mice at single oral doses.

Lactation

Limited date from case reports demonstrate that a small amount of mebendazole is present in human milk following oral administration. VERMOX® 500 mg is not recommended during lactation.

Fertility

The effect on human fertility has not been evaluated.

4.7 Effects on ability to drive and use machines

VERMOX® 500 mg can cause side effects such as dizziness. Caution is advised before driving a vehicle or operating machinery until the effects of VERMOX® 500 mg are known.

4.8 Undesirable effects

Patients with high parasitic burdens when treated with VERMOX® 500 mg have manifested diarrhea and abdominal pain.

Clinical trial data

The safety of VERMOX® 500 mg 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 VERMOX® 500 mg-treated subjects. ADRs occurring in ≤ 1% of VERMOX®-treated subjects are shown below.

Blood and the lymphatic system disorders

Less frequent: agranulocytosis (higher and prolonged doses)

Nervous system disorders

Less frequent: dizziness

Gastrointestinal disorders

Frequent: abdominal pain

Less frequent: abdominal discomfort, diarrhoea, flatulence

Skin and subcutaneous tissue disorders

Less frequent: rash

Renal and urinary disorders

Less frequent: glomerulonephritis (higher and prolonged doses)

Post-marketing

Blood and the lymphatic system disorders

Less frequent: neutropenia

Immune system disorders

Less frequent: hypersensitivity including anaphylactic reaction and anaphylactoid reaction

Nervous system disorders

Less frequent: convulsions

Gastrointestinal disorders

Less frequent: nausea, vomiting

Hepato-biliary disorders

Less frequent: hepatitis, abnormal liver function tests

Skin and subcutaneous tissue disorders

Less frequent: toxic epidermal necrolysis, Stevens Johnson syndrome, exanthema, angioedema, urticaria, alopecia

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of VERMOX® 500 mg tablets is important. It allows continued monitoring of the benefit/risk balance of VERMOX® 500 mg tablets. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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: 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 VERMOX® 500 mg tablets at standard dosages.

Symptoms

In the event of accidental overdose, abdominal cramps, nausea, vomiting and diarrhoea may occur.

Treatment

There is no specific antidote. If poisoning or excessive overdosage is suspected it is

recommended, on general principles, that vomiting be induced and such symptomatic supportive therapy be administered as appears indicated. Activated charcoal may be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.12 Anthelmintics, bilharzia medicines, filaricides, etc.

Pharmacotherapeutic group: Anthelmintic for oral administration, benzimidazole derivatives.

ATC code: P02 CA01.

Mebendazole is a broad-spectrum anthelmintic.

Mebendazole acts locally in the lumen of the gut by interfering with cellular tubulin formation in the intestines of worms. Mebendazole binds specifically to tubulin and causes ultrastructural degenerative changes in the intestine. As a result, the glucose uptake and the digestive functions of the worm are disrupted to such as extent that an autolytic process occurs.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, < 10 % of the dose reaches the systemic circulation, due to incomplete absorption and to extensive pre-systemic metabolism (first-pass effect).

Maximum plasma concentrations are generally seen 2 to 4 hours after administration. Dosing with a high fat meal increases 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 3 – 21 months) that show medicine levels in tissue.

Biotransformation

Orally administered mebendazole is extensively metabolised primarily by the liver. Plasma concentrations of its major metabolites (hydrolysed and reduced forms of mebendazole) are 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

corn starch,

magnesium stearate (E572),

methylcellulose,

microcrystalline cellulose (E460(i)),

silicon dioxide (E551),

sodium starch glycolate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

Store at or below 25 ºC.

6.4 Special precautions for storage

Keep in the original container until required for use.

6.5 Nature and contents of container

Carton containing one blister pack of 1 tablet.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Johnson & Johnson (Pty) Ltd.

241 Main Road

Retreat

7945

South Africa

8. REGISTRATION NUMBER

W/12/42

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/11/1990

10. DATE OF REVISION OF THE TEXT

To be allocated by SAHPRA.

EXPORT REGISTRATION DETAILS:

Kenya: 3457

Malawi: PMPB/PL353/16

Namibia: 04/12/0263 NS1

Tanzania: TAN00, 127 P02X JAN

Uganda: 3451/06/00

Zambia: 009/003 P

Zimbabwe: 91/7.7/2437 P