**Summary of Product Characteristics for Pharmaceutical Products**

## 1. Name of the medicinal product

ALVER Tablet

## 2. Qualitative and quantitative composition

Each uncoated chewable tablets contains:
Ivermectin BP 6 mg
Albendazole USP 400 mg

Excipients with known effect:: Each uncoated tablet of contains 8mg aspartame, 60mg lactose, 0.075mg methyl Hydroxybenzoate and 0.015mg propyl hydroxybenzoate.

For full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Uncoated chewable tablet.
White to off white, elongated, biconvex, scored on one side, uncoated chewable tablets.

## 4. Clinical particulars

### 4.1 Therapeutic indications

The treatment of Hymenolepis nana and Taenia spp. (tapeworm) infections, when other susceptible helminths species are present.

### 4.2 Posology and method of administration

**Route of administration**

Oral

**Nematode infestations**

Adult: contains ivermectin 3 or 6 mg and Albendazole 400 mg: daily dose.

Onchoocerciasis:
Adult- >= 15 kg: 150 mcg/kg as a single dose every 6-12 months until asymptomatic.

Child- >five years >= 15kg: 150 mcg/kg as a single dose every 6-12 months until asymptomatic.

Strongyloidiasis
Adult- >= kg kg: 200 mcg/ kg once daily for 1-2 days.
For immunocompromised patients: May need to repeat dose every 2-4 weeks.

Child: > 15 kg 200mcg/ kg as a single dose or daily on a two consecutive days.
For immunocompromised patients: May need to repeat dose every two to four weeks.

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

**Uncovering pre-existing neurocysticercosis**

Treatment with albendazole may uncover pre-existing neurocysticercosis, particularly in areas with high taenia infection. Patients may experience neurological symptoms such as seizures, increased intracranial pressure and focal signs as a result of an inflammatory reaction caused by death of the parasite within the brain. Symptoms may occur soon after treatment, and appropriate steroid and anticonvulsant therapy should be started.

**Risk of retinal damage in patients with retinal neurocysticercosis**

Cysticercosis may, in rare cases, involve the retina. Before initiating therapy for neurocysticercosis, the patient should be examined for the presence of retinal lesions. If such lesions are visualised, the need for anticysticeral therapy should be weighed against the possibility of retinal damage caused by albendazole- induced changes to the retinal lesion.

**Hepatic effects**

Mild to moderate elevations of liver enzymes have been reported with albendazole. In prolonged higher dose albendazole therapy for hydatid disease there have been rare reports of severe hepatic abnormalities such as jaundice and histological hepatocellular damage, which may be irreversible. Enzyme abnormalities are usually reversible on discontinuation of treatment.

Patients with disturbed liver function tests prior to commencing albendazole therapy should be carefully evaluated, since the medicine is metabolised by the liver and has been associated with idiosyncratic hepatotoxicity. If enzymes are significantly increased (greater than twice the upper limit of normal) during treatment, [NT005 trade name] should be discontinued. [NT005 trade name] treatment may be reinstituted when levels have returned to normal limits, but liver function should be monitored frequently during repeat therapy.

**Bone marrow suppression**

Albendazole can cause bone marrow suppression and therefore blood counts are needed at the start and every two weeks during each 28 day

cycle for treating echinococcosis. Patients with liver disease, including hepatic echinococcosis, may be more susceptible to bone marrow suppression leading to pancytopenia, aplastic anaemia, agranulocytosis and leucopenia and therefore warrant closer monitoring of blood counts. Albendazole should be discontinued if clinically significant decreases in blood cell counts occur.

Ivermectin is not a prophylactic therapy for filarial infection or strongyloidiasis. It has not been shown to be effective in killing adult filariae.

Ivermectin does not have any beneficial effect on tropical pulmonary eosinophilia syndrome, on lymphadenitis or on lymphangitis associated with filarial infections.

Ivermectin should not be given to patients who are seriously ill. An assessment of health status is recommended before treatment to exclude seriously ill individuals.

**Loaiasis**

Following administration of ivermectin, the intensity and severity of adverse effects are probably related to the pre-treatment microfilarial density. In patients co-infected with Loa loa, microfilarial density, particularly in the blood, is most often high which predisposes the treated patients to an increased risk of serious adverse effects.

CNS adverse effects (encephalopathies) have been reported in rare cases in patients treated with ivermectin and co-infected by a high number of microfilariae of Loa loa (see section 4.8). Consequently, in Loa loa endemic areas, ivermectin is not recommended as part of programmes to treat lymphatic filariasis and special measures should be taken before any onchocerciasis treatment with ivermectin.

**Mazzoti reaction**

Following administration of medicines with a rapid microfilaricidal action in patients with onchocerciasis, cutaneous and systemic reactions of varying severity (the Mazzotti reaction), and ophthalmological reactions have been reported. These reactions are probably due to inflammatory responses to degradation products released by the death of microfilariae. Patients treated with ivermectin for onchocerciasis may also experience these reactions when treated for the first time.

Patients with hyperreactive onchodermatitis or “sowda” (observed particularly in Yemen) are more likely than others to experience severe cutaneous adverse reactions (oedema and aggravation of onchodermatitis) after treatment with microfilaricidal medicines.

**Immunocompromised patients**

Efficacy and dosing regimen of ivermectin in immunocompromised

patients with intestinal strongyloidiasis have not been established by adequate clinical studies. There have been cases which show the persistence ofinfestation following a single dose of ivermectin, particularly in this type of patient.

**Children**

Ivermectin is not recommended for use in children less than 90 cm tall or weighing less than 15 kg.

**Pregnancy and breast-feeding**

Ivermectin should not be used during pregnancy or in lactating women for the first week after birth (see section 4.6).

## 4.5 Interaction with other medicinal products and other forms of interaction

Dexamethasone, praziquantel and cimetidine may increase the plasma concentration of the active metabolite of albendazole, albendazole sulphoxide.

Ritonavir, phenytoin, carbamazepine and phenobarbital may have the potential to reduce plasma concentrations of the active metabolite of albendazole. The clinical relevance of this is unknown, but may result in decreased efficacy, especially in the treatment of systemic helminth infections. Patients should be monitored for efficacy and may require alternative dose regimens or therapies.

Interactions between ivermectin and other medicines have not been studied in clinical trials.
There have been rare post-marketing reports of increased INR (International Normalised Ratio) when ivermectin was given with warfarin.

## 4.6 Fertility, pregnancy, and lactation

Women of childbearing potential
Pregnancy should be avoided in women treated with albendazole. Adequate contraceptive measures should be taken.

**Albendazole**
Pregnancy
There are no adequate and well-controlled studies of albendazole administration in pregnant women. Animal studies have revealed evidence of teratogenicity in rats and rabbits (see section 5.3).

Albendazole should be used in pregnant women only if there are no alternatives and the potential benefit justifies the potential risk to the fetus.

Lactation
Albendazole acts primarily in the intestinal system of the mother and little is absorbed systemically; therefore, it is compatible with breastfeeding.

Fertility
There are no data on the effects of albendazole on human male or female fertility. Animal studies indicate no effects of albendazole on fertility (see section 5.3).

**Ivermectin**

**Pregnancy**
There are no adequate and well-controlled studies of ivermection administration in pregnant women. Animal studies have revealed evidence of teratogenicity (see section 5.3). Ivermectin should only be used when strictly indicated.

**Breastfeeding**
Ivermectin passes into human milk in low concentrations. Treatment of mothers who intend to breast-feed should only be undertaken when the risk of delayed treatment to the mother outweighs possible risk to the newborn.
In mass administration programmes for community suppression, women who are breast-feeding should not be given ivermectin during the first week after giving birth.

**Fertility**
No human data on the effect of ivermectin on fertility are available. Ivermectin had no adverse effects on the fertility in rats (see section 5.3).

## 4.7 Effects on ability to drive and use machines.

**Albendazole**
Patients should be warned about the potential for dizziness (see sections 4.8) while taking albendazole and should be advised not to drive or operate machines if this occurs.

**Ivermectin**
The effect of ivermectin on the ability to drive and use machines has not been studied. Some patients may get side effects such as dizziness, somnolence, vertigo and tremor, which could affect the ability to drive or use machines (see section 4.8). Patients should be advised not to drive or operative machines until any such effects have resolved.

## 4.8 Undesirable effects

**Albendazole**
Data from clinical trials and post-marketing surveillance were used to estimate the frequency of adverse events linked to albendazole.
The adverse reactions considered related to albendazole are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000), and very rare (< 1/10 000).

## Short duration of treatment

Blood and the lymphatic system disorders

| | |
|---|---|
| Rare | Low red cell count |

Immune system disorders

| | |
|---|---|
| Rare | Hypersensitivity reactions including rash, pruritus and urticaria |

Nervous system disorders

| | |
|---|---|
| Uncommon | Headache, dizziness |

Gastrointestinal disorders

| | |
|---|---|
| Common | Upper gastrointestinal symptoms (e.g. epigastric or abdominal pain, nausea, vomiting) |
| Uncommon | Diarrhoea |

Hepatobiliary disorders

| | |
|---|---|
| Rare | Elevations of hepatic enzymes |

Skin and subcutaneous tissue disorders

| | |
|---|---|
| Uncommon | Itchiness, skin rashes |
| Very rare | Erythema multiforme, Stevens-Johnson syndrome |

Musculoskeletal and connective tissue disorders

| | |
|---|---|
| Rare | Bone pain |

Renal and urinary disorders

| | |
|---|---|
| Rare | Proteinuria |

## Longer duration of treatment

Blood and the lymphatic system disorders

| | |
|---|---|
| Uncommon | Leucopenia |
| Rare | Low red cell count |
| Very rare | Pancytopenia, aplastic anaemia, agranulocytosis |

Immune system disorders

| | |
|---|---|
| Uncommon | Hypersensitivity reactions including rash, pruritus and urticaria |

Nervous system disorders

| | |
|---|---|
| Very common | Headache |
| Common | dizziness |

Gastrointestinal disorders

| | |
|---|---|
| Common | Gastrointestinal disturbances (abdominal pain, nausea, vomiting) |

Hepatobiliary disorders

| | |
|---|---|
| Very common | Mild to moderate elevations of hepatic enzymes |
| Uncommon | Hepatitis[1] |

Skin and subcutaneous tissue disorders

| | |
|---|---|
| Common | Reversible alopecia (thinning of hair, and moderate hair loss) |
| Very rare | Erythema multiforme, Stevens-Johnson syndrome |

| | |
|---|---|
| Musculoskeletal and connective tissue disorders | |
| Rare | Bone pain |
| Renal and urinary disorders | |
| Rare | Proteinuria |
| General disorders | |
| Common | Fever |

[1] With prolonged albendazole treatment for hydatid disease there have also been reports of severe hepatic abnormalities, including jaundice and hepatocellular damage which may be irreversible

**Ivermectin**

Transient eosinophilia, liver dysfunction (hepatitis), increased liver enzymes, hyperbilirubinemia and haematuria have been reported.

Very rarely, toxic epidermal necrolysis and Stevens-Johnson syndrome have also been reported.

**Filarial infections**

Ivermectin is generally well-tolerated in the management of onchocerciasis. Side effects are related to the parasite density and are mild and transient in most cases, but their severity may be increased in patients infected with more than one parasite, particularly in the case of infestation with Loa loa.

Following administration of ivermectin, Mazzotti-type hypersensitivity reactions due to microfilarial death have been reported: pruritus, urticarial rash, conjunctivitis, arthralgia, myalgia (including abdominal myalgia), fever, oedema, lymphadenitis, adenopathies, nausea, vomiting, diarrhoea, orthostatic hypotension, vertigo, tachycardia, asthenia, headache. Rarely, these side effects can be severe. A few cases of asthma exacerbation have occurred.

Abnormal sensation in the eyes, eyelid oedema, anterior uveitis, conjunctivitis, limbitis, keratitis and chorioretinitis or choroiditis can also occur occasionally, but may also be due to the disease itself. They generally resolved without corticosteroid treatment.

In clinical trials involving 963 adults with onchocerciasis given ivermectin 100–200 micrograms/kg, reactions were reported with the following frequency in the first few days after treatment:

| **Adverse reaction[a]** | **Ivermectin** | **Placebo** |
|---|---|---|
| Pruritus | 27.5% | 17.2% |
| Rash including urticarial rash | 22.7% | 9.2% |
| Fever | 22.6% | 4.8% |
| Lymph node enlargement - axillary | 11.0% | 2.9% |

| | | |
|---|---|---|
| - cervical | 5.3% | 4.1% |
| - inguinal | 12.6% | 6.7% |
| - other | 3.0% | 1.6% |
| Lymph node tenderness - axillary | 4.4% | 1.0% |
| - cervical | 1.2% | 0.6% |
| - inguinal | 13.9% | 5.7% |
| - other | 1.9% | 0.6% |
| Arthralgia/synovitis | 9.3% | 4.4% |
| Limbitis | 5.5% | 6.2% |
| Punctate opacity | 1.8% | 2.0% |
| Peripheral oedema | 3.2% | 0.6% |
| Facial oedema | 1.2% | 0.0% |
| Tachycardia | 3.5% | 0.6% |
| Orthostatic hypotension | 1.1% | 0.0% |

a The most common adverse effects reported in these trials, regardless of causality, were headache (22.3%) and myalgia (19.7%) but headache and myalgia assessed as related to treatment occurred in less than 1% of patients given ivermectin.

Rarely, severe and potentially fatal encephalopathy can occur after administration of ivermectin, particularly in patients also heavily infected with Loa loa. In these patients, the following adverse reactions have also been reported: back or neck pain, ocular hyperaemia, subconjunctival haemorrhage, dyspnoea, urinary and faecal incontinence, difficulty in standing or walking, mental status changes, confusion, lethargy, stupor or coma (see section 4.4).
Onset of conjunctival haemorrhage has been reported post-marketing in patients with onchocerciasis.
In the treatment of lymphatic filariasis, the following have occurred: fever, headache, asthenia, feeling of weakness, myalgia, arthralgia, diffuse pain, digestive disorders such as anorexia, nausea, abdominal and epigastric pain, cough, feeling of respiratory discomfort, sore throat, orthostatic hypotension, chills, vertigo, profuse sweating, testicular pain or feeling of discomfort.

**Strongyloidiasis**
In studies in patients receiving ivermectin for the treatment of strongyloidiasis, dizziness (2.8%), pruritus (2.8%), diarrhoea and nausea (both 1.8%) have been reported commonly; vomiting, constipation, anorexia, abdominal pain, asthenia or fatigue, somnolence, vertigo, tremor, and leucopenia and anaemia were reported in less than 1% of patients.

**Scabies**
In patients with scabies, pruritus may be exacerbated at the start of treatment. Patients should be warned that itching may persist for one to two

weeks after treatment, even if the mite is successfully eradicated. Other reported reactions are uncommon (<1%) and include headache (<1%), arthralgia (< 1%) and anorexia as well as lethargy, listlessness, abdominal discomfort, rash, and dizziness. Adult Ascaris expulsion has been observed following ingestion of ivermectin.

**Reporting of suspected adverse reactions:** Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

### 4.9 Overdose

**Albendazole**
In case of overdosage, symptomatic therapy and general supportive measures are recommended.

**Ivermectin**
Cases of accidental overdose with ivermectin have been reported, but none have resulted in fatalities.
In cases of accidental intoxication with unknown doses of products destined for veterinary use (oral use, as an injection, cutaneous use), the symptoms were: rash, contact dermatitis, oedema, headache, vertigo, asthenia, nausea, vomiting, diarrhoea and abdominal pain. Other effects include: seizures, ataxia, dyspnoea, paraesthesia and urticaria.

Management has been with symptomatic treatment and surveillance in a medical care setting with fluid replacement and blood pressure management, if necessary. Although there are no specific studies available, it is advisable to avoid GABA agonists in the treatment of accidental intoxication with ivermectin.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

**Albendazole**
Pharmacotherapeutic group: Antihelmintics, benzimidazole derivatives, ATC code: P02CA03.
Mechanism of action
Albendazole is a benzimidazole derivative that causes degenerative alterations in the tegument and intestinal cells of the parasite and blocks their energy production, ultimately leading to immobilisation and death of the parasite. It works by binding to the colchicine-sensitive site of tubulin, thus inhibiting its assembly into microtubules. As cytoplasmic microtubules are critical in promoting glucose uptake, the glycogen stores of the parasites are depleted.

**Ivermectin**

Pharmacotherapeutic group: Anthelmintics, ATC code: P02CF01.

Ivermectin is derived from avermectins isolated from fermentation broths of Streptomyces avermitilis. It has high affinity for glutamate-gated chloride channels in invertebrate nerve and muscle cells. Its binding to these channels promotes an increase in membrane permeability to chloride ions, leading to hyperpolarisation of the neural or muscle cell. This results in neuromuscular paralysis and may lead to the death of certain parasites.

Ivermectin also interacts with other ligand-gated chloride channels such as the one involving the GABA (gamma-aminobutyric acid) neurotransmitter. Mammals do not have glutamate-gated chloride channels. Avermectins have only low affinity for other ligand-gated chloride channels. They do not readily cross the blood–brain barrier.

## 5.2 Pharmacokinetic properties

**Pharmacokinetics of albendazole**

| | |
|---|---|
| **General** | |
| | Albendazole concentrations are negligible or undetectable in plasma as itis rapidly converted into the sulfoxide metabolite prior to reaching the systemic circulation. The systemic anthelmintic activity has been attributed to this primary metabolite, albendazole sulfoxide.<br>Maximal plasma concentrations of albendazole sulfoxide are typicallyachieved 2 to 5 hours after dosing. |
| **Absorption** | |
| Absolute bioavailability | NA* |
| Oral bioavailability | Albendazole is poorly absorbed from the gastrointestinal tract (<5%) dueto its low aqueous solubility. |
| Food effect | Absorption is significantly enhanced (approximately 5-fold) ifalbendazole is administered with a fatty meal. |
| **Distribution** | |
| Volume of distribution (mean) | NA* |
| Plasma protein binding invitro | Albendazole sulfoxide is 70% bound to plasma protein. |
| Tissue distribution | Albendazole sulfoxide is widely distributed throughout the body; it hasbeen detected in urine, bile, liver, cyst wall, cyst fluid, and cerebral spinal fluid. |

| | |
|---|---|
| **Metabolism** | |
| | Albendazole rapidly undergoes extensive first-pass metabolism in the liver to albendazole sulfoxide, and is generally not detected in plasma. Albendazole sulfoxide is further metabolized to albendazole sulfone andother primary oxidative metabolites. |
| Active metabolite(s) | Albendazole sulfoxide |
| **Elimination** | |
| Elimination half life | The terminal elimination half-life of albendazole sulfoxide typicallyranges from 8 to 12 hours. |
| Mean systemic clearance(Cl/F) | |
| Excretion | Following oral administration, albendazole has not been detected in human urine. Albendazole sulphoxide and its metabolites appear to be principally eliminated in bile, with only a small proportion appearing in the urine. |

| | |
|---|---|
| Pharmacokinetic linearity | Plasma concentrations of albendazole sulfoxide increase in a dose-proportional manner over the therapeutic dose range following ingestion of a fatty meal. |
| Drug interactions (in vitro) | |
| Transporters | NA* |
| Metabolizing enzymes | NA* |

## Special populations

Renal impairment
Since renal elimination of albendazole and its primary metabolite, albendazole sulfoxide, is negligible, it is unlikely that clearance of these compounds would be altered in these patients.

Liver impairment
In patients with evidence of extrahepatic obstruction, the systemic availability of albendazole sulfoxide was increased 7-fold.

Elderly patients
Although no studies have investigated the effect of age on albendazole sulfoxide pharmacokinetics, data suggest that the pharmacokinetics is similar to those in young healthy subjects.

Paediatrics
Following single-dose administration of 200 to 300 mg (approximately 10 mg/kg) albendazole to paediatric patients with hydatid cyst disease (age range

6 to 13 years), albendazole sulfoxide pharmacokinetics were similar to those observed in fed adults.

Absorption of Ivermectin
The absorption characteristics of Ivermection have been determined after administration of one (1) tablet in healthy volunteers in the fasted state as follows:

| **Pharmacokinetic variable** | **Arithmetic mean ±standard deviation (*)** |
|---|---|
| | **Ivermectin** |
| Maximum concentration (Cmax) | 16.5 ± 5.9 (16.3) ng/mL |
| Area under the curve (AUC0-∞), a measure of the extent of absorption | 374 ± 144 ng.h/mL |
| Time to attain maximum concentration (tmax) | 4.38 ± 1.24 h |

*geometric mean

**Pharmacokinetics of ivermectin**

| | |
|---|---|
| **General** | |
| | Ivermectin contains 2 components, H2B1a and H2B1b, of which H2B1a is the major component (> 90%). |
| **Absorption** | |
| Absolute bioavailability | NA |
| Oral bioavailability | NA |
| Food effect | Administration with a high-fat meal results in approximately 2.5-fold increase in bioavailability relative to the fasted state. |
| **Distribution** | |
| Volume of distribution (mean) | NA |
| Plasma protein binding | NA |
| Tissue distribution | NA |
| **Metabolism** | |
| | Metabolised in the liver, mainly by CYP3A4, and possibly to a lesser extent by CYP2D6 and CYP2E1. |
| Active metabolite(s) | NA |
| **Elimination** | |
| Elimination half life | ~18 h |
| Mean systemic clearance (Cl/F) | NA |
| % of dose excreted in urine | <1% |
| % of dose excreted in faeces | 99% |
| **Pharmacokinetic linearity** | The plasma concentration increases with increasing doses in a generally<br>proportional manner. |

| **Drug interactions (in vitro)** | |
|---|---|
| Transporters | NA |
| Metabolizing enzymes | Studies suggest that ivermectin at standard oral doses does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP1A6 or CYP2E1. |

NA: information not available

Hepatic and renal impairment
The pharmacokinetics of ivermectin has not been studied in patients with impaired hepatic or renal function.

## 5.3 Preclinical safety data

**Albendazole**
**General toxicity**
Studies of up to 6 months in mice, rats and dogs recognised the haematopoietic system and the liver as target organs of toxicity.

**Genotoxicity**
In genotoxicity tests, albendazole was found negative in an Ames Salmonella/microsome plate mutation assay, Chinese hamster ovary chromosomal aberration test, and in vivo mouse micronucleus test. In the in vitro BALB/3T3 cells transformation assay, albendazole produced weak activity in the presence of metabolic activation while no activity was found in the absence of metabolic activation.

**Carcinogenicity**
Long-term carcinogenicity studies in mice and rats found no evidence of increased incidence of tumours was found in the mice or rats at up to 400 mg/kg/day and 20 mg/kg/day, respectively.

**Toxicity to reproduction**
Albendazole did not affect male or female fertility in the rat at an oral dose level of 30 mg/kg/day.

Albendazole has been shown to be teratogenic (to cause embryotoxicity and skeletal malformations) in pregnant rats and rabbits. The teratogenic response in the rat was shown at oral doses of 10 and
30 mg/kg/day during gestation days 6 to 15, and in pregnant rabbits at oral doses of 30 mg/kg/day administered during gestation days 7 to 19. In the rabbit study, maternal toxicity (33% mortality) was noted at 30 mg/kg/day. In mice, no teratogenic effects were observed at oral doses up to 30 mg/kg/day administered during gestation days 6 to 15.

**Ivermectin**
**General toxicity**
Studies in animals showed that the main effects of ivermectin were attributed to its effects on the central nervous system (mydriasis, tremors, ataxia, anorexia).
**Genotoxicity**

Ivermectin was not genotoxic in vitro in the Ames microbial mutagenicity assay of Salmonella typhimurium strains TA1535, TA1537, TA98, and TA100 with and without rat liver enzyme activation, the Mouse Lymphoma Cell Line L5178Y (cytotoxicity and mutagenicity) assays, or the unscheduled DNA synthesis assay in human fibroblasts.

**Carcinogenicity**

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ivermectin.

**Reproductive toxicity**

Ivermectin had no adverse effects on the fertility in rats in studies at repeated doses of up to 3 times the maximum recommended human dose of 200 micrograms/kg (on a $mg/m^2$/day basis).

Ivermectin has been shown to be teratogenic in mice, rats, and rabbits when given in repeated doses of 0.2, 8.1, and 4.5 times the maximum recommended human dose, respectively (on a $mg/m^2$/day basis).

Teratogenicity was characterized in the three species tested by cleft palate; clubbed forepaws were additionally observed in rabbits. These developmental effects were found only at or near doses that were maternotoxic to the pregnant female. Therefore, ivermectin does not appear to be selectively fetotoxic to the developing fetus.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Maize Starch
Microcrystalline Cellulose
Aspartame
Lactose
Methyl Hydroxybenzoate
Propyl Hydroxybenzoate
Povidone (PVPK-30)
Purified Water
Purified Talc
Magnesium Stearate
Flavour Mango
Hydrophobic colloidal anhydrous silica

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store below 30°C.

### 6.5 Nature and contents of container

1 tablet in a Alu-PVC blister and such 1 blister packed in carton with package insert.

### 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 authorization holder and manufacturing site addresses

**Marketing authorization holder:**

Next Wave (India)
SCO No. 313, Second Floor,
Sector 29, Gurugram, 122009, Haryana, India.
Telephone No.: +91-124-4212295, 4057980
Fax: +91-124-3292980
Email: info@nextwaveindia.in

**Manufacturing site address:**

Next Wave (India)
Rampur Ghat Road, Paonta Sahib
Distt. Sirmour, H.P.-173025
India
Telefax: +91-01704-223215
Email: info@nextwaveindia.in

## 8. Marketing authorization number

CTD9437

## 9. Date of first registration

04-Aug-2023

## 10. Date of revision of the text

16-Sep-23

## 11. Dosimetry

Not Applicable

## 12. Instructions for Preparation of Radiopharmaceuticals

Not Applicable