IVERMECTIN BENTA®

Ivermectin

FORMS AND PRESENTATION
Ivermectin Benta®: Tablets: Box of 6 and 10.

COMPOSITION
Ivermectin Benta®: Each tablet contains Ivermectin 6 mg.
Excipients: Microcrystalline Cellulose, Mannitol, Croscarmellose Sodium, Colloidal Silicon Dioxide, Butylated hydroxyanisol, Pregelatinised Starch, Magnesium Stearate

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: ATC code: P02CF01
Anthelmintic.
Ivermectin is derived from the avermectins, that are isolated from fermentation of Streptomyces avermitilis. It binds selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite.
Ivermectin interacts also with other ligand-gated chloride channels, such as those gated by the neurotransmitter gammaaminobutyric acid (GABA).
Mammals do not have glutamate-gated chloride channels. The avermectins have a low affinity for mammalian ligandgated chloride channels. They do not readily cross the blood-brain barrier in humans. Treatment with a single dose of 200 µg/kg ivermectin has been shown to be effective and well-tolerated in patients with a normal immunity and for whom infestation by Strongyloides stercoralis is limited to the digestive tract.

PHARMACOKINETIC PROPERTIES
With 12 mg single oral doses of Ivermectin administered as tablets, the mean peak plasma concentration of the major component (H2B1a) was 46.6 (± 21.9) ng/mL at approximately 4 hours after dosing.
Plasma concentration increases with increasing dose in a manner approximately proportional to the dose. Ivermectin is metabolized in humans, and ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 hours with less than 1% of the administered dose being excreted in the urine. The plasma half-life of ivermectin in man is about 12 hours and that of the metabolites is about 3 days.
In vitro studies have shown that ivermectin is primarily metabolized by CYP3A4. Preclinical studies suggest that ivermectin has limited potential to inhibit CYP3A4 at clinical doses and no potential to inhibit other CYP enzymes (2D6, 2C9, 1A2, and 2E1).
A multiple-dose (30 to 120 mg [333 to 2000 mcg/kg]) clinical safety study has been conducted to assess the safety and pharmacokinetic properties of ivermectin in healthy volunteers. Subjects received oral doses of 30 to 120 mg (333 to 2000 mcg/kg) ivermectin in a fasted state or 30 mg (333 to 600 mcg/kg) ivermectin following a standard high-fat (48.6 g of fat) meal. Administration of 30 mg ivermectin following a high-fat meal resulted in an approximate 2.5-fold increase in bioavailability relative to administration of 30 mg ivermectin in the fasted state. However, there were no indications of central nervous system toxicity associated with either regimen.

INDICATIONS
- Treatment of intestinal strongyloidiasis (anguillulosis).
- Treatment of proven suspected microfilaraemia in patients with lymphatic filariasis caused by Wuchereria bancrofti.
- Treatment of human sarcoptic scabies after prior treatment has failed. Treatment is justified when the diagnosis of scabies has been established clinically and/or by parasitological examination. Without formal diagnosis, treatment is not justified in case of pruritus.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients used in this formulation.

WARNINGS AND PRECAUTIONS
Efficacy and dosing regimen of ivermectin in immunocompromised patients being treated for intestinal strongyloidiasis have not been established by adequate clinical studies. There have been reported cases which show the persistence of infestation following a single dose of ivermectin particularly in these types of patients.
Ivermectin is not a prophylactic therapy of infection with filariae or anguillulosis; there are no data available demonstrating the efficacy of ivermectin either for killing or preventing the maturation of infective larvae in humans.
Ivermectin has not been shown to have any activity against the adult worm of any species of Filariae.
Ivermectin has not been shown to have any beneficial effect on tropical pulmonary eosinophilia syndrome on lymphadenitis or lymphangitis observed in case of infection with filariae.
Following administration of ivermectin, the intensity and severity of adverse experiences are probably related to the pre-treatment microfilarial density particularly in the blood. 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 in the occurrence of serious adverse experiences.
CNS adverse experiences (encephalopathies) have been rarely reported in patients treated with ivermectin and co-infected by a high number of microfilariae of Loa loa. Consequently, in Loa loa endemic areas, special measures should be taken before any treatment with ivermectin.
Following administration of drugs with a rapid microfilaricidal action such as DEC in patients with onchocerciasis, cutaneous and/or 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 following the death of microfilariae.
Patients treated with ivermectin for onchocerciasis may also experience these reactions when treated for the first time.
After treatment with a microfilaricidal drug, patients with hyper-reactive onchodermatitis may be more likely than others to experience severe cutaneous adverse reactions (oedema and aggravation of onchodermatitis).

Pediatric Population
Safety in pediatric patients weighing less than 15 kg of body weight has not been established.

DRUG INTERACTIONS
The effects of some drugs can change if you take other drugs or herbal products at the same time. This can increase your risk for serious side effects or may cause your medications not to work correctly. These drug interactions are possible, but do not always occur. Your doctor or pharmacist can often prevent or manage interactions by changing how you use your medications or by close monitoring.
Some of the products that may interact with this drug include: barbiturates (such as phenobarbital, butalbital), benzodiazepines (such as clonazepam, lorazepam), sodium oxybate (GHB), valproic acid.

ADVERSE EFFECTS
Side effects are related to the microfilarial density and most of them are mild and transient in nature but the incidence and severity may be higher in patients infected with more than one parasite, as in the case of infection with Loa loa.
Rarely, patients who are also heavily infected with Loa loa may develop a serious or even fatal encephalopathy following treatment with ivermectin. In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival haemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma.
In the treatment of strongyloidiasis, the following side effects have been reported after ivermectin therapy: asthenia, abdominal pain, anorexia, constipation, diarrhea, nausea, vomiting, dizziness, somnolence, vertigo, tremor, transient eosinophilia, leukopenia/anemia and increase in ALT/alkaline phosphatases.

In the treatment of filariasis caused by Wuchereria bancrofti, the intensity of the side effects does not seem to be dose-related but is related to the blood microfilarial density. The following have been reported: fever, headache, asthenia, feeling of weakness, myalgia, arthralgia, body pain, digestive disorders such as anorexia, nausea, abdominal and epigastric pain, cough, feeling of respiratory discomfort, sore throat, postural hypotension, chills, vertigo, diaphoresis,
testicular pain or feeling of discomfort.

Following treatment of patients infected with Onchocerca volvulus with ivermectin, the following hypersensitivity reactions may occur due to the death of microfilariae: these are symptoms of Mazzotti type reactions: pruritus, frank urticarial rash, conjunctivitis, arthralgia, myalgia (including abdominal myalgia), fever, oedema, lymphadenitis, lymphadenopathies, nausea, vomiting, diarrhea, orthostatic hypotension, vertigo, tachycardia, asthenia, headache.
These reactions have been rarely severe. Some cases of worsening of bronchial asthma have been reported. In these patients, abnormal

sensation in eyes, eyelid oedema, anterior uveitis, conjunctivitis, limbitis, keratitis and chorioretinitis or chorioditis, have also been described. These reactions can occur due to the disease itself, but have occasionally been reported after therapy. These have rarely been severe and have generally resolved without corticosteroid treatment.
Transient hypereosinophilia, liver function abnormalities and haematuria have been reported.
Cases of ascaris expulsion of adult worms have been described following administration of ivermectin.
In patients with scabies, transient exacerbation of pruritus may be noted at the beginning of treatment.

Post Marketing Experience
Onchocerciasis
Conjunctival haemorrhage

All indications
Very rarely, hypotension (mainly orthostatic hypotension), worsening of bronchial asthma, toxic epidermal necrolysis,Stevens-Johnson syndrome, seizures, hepatitis, elevation of liver enzymes, and elevation of bilirubin.

DOSAGE AND ADMINISTRATION
Posology
Oral use

Usual Adult Dose of Ivermectin for Onchocerciasis:
0.15 mg/kg orally once every 12 months
Patients with heavy ocular infection may require retreatment every 6 months. Retreatment may be considered at intervals as short as 3 months.
Dosage guidelines based on body weight:
15 to 25 kg: 3 mg orally one time
26 to 44 kg: 6 mg orally one time
45 to 64 kg: 9 mg orally one time
65 to 84 kg: 12 mg orally one time
85 kg or more: 0.15 mg/kg orally one time

Usual Adult Dose for Strongyloidiasis:
0.2 mg/kg orally once
In immunocompromised (including HIV) patients, the treatment of strongyloidiasis may be refractory requiring repeated treatment (i.e., every 2 weeks) and suppressive therapy (i.e., once a month), although well-controlled studies are not available. Cure may not be achievable in these patients.
Dosage guidelines based on body weight:
15 to 24 kg: 3 mg orally one time
25 to 35 kg: 6 mg orally one time
36 to 50 kg: 9 mg orally one time
51 to 65 kg: 12 mg orally one time
66 to 79 kg: 15 mg orally one time
80 kg or more: 0.2 mg/kg orally one time

Usual Adult Dose for Ascariasis:
0.2 mg/kg orally once

Usual Adult Dose for Cutaneous Larva Migrans:
0.2 mg/kg orally once

Usual Adult Dose for Filariasis:
0.2 mg/kg orally once

Bancroftian filariasis: 0.4 mg/kg orally once yearly (with a single annual dose of diethylcarbamazine 6 mg/kg), for 4 to 6 years .

Usual Adult Dose for Scabies:
0.2 mg/kg orally once, and repeated in 2 weeks
Ivermectin therapy may be combined with a topical scabicide.

Usual Pediatric Dose for Filariasis:
Bancroftian filariasis:
5 years or older: 0.4 mg/kg orally once yearly (with a single annual dose of diethylcarbamazine 6 mg/kg) for 4 to 6 years

OVERDOSE
There are reports of accidental overdosage of ivermectin, but no fatalities have been attributable to ivermectin overdosing.
In accidental intoxication with unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, injection, exposure to body surfaces, the following symptoms have been reported: rash, contact dermatitis, oedema, headache, vertigo, asthenia, nausea, vomiting, diarrhea, and abdominal pain. Other adverse effects that have been reported include: seizures, ataxia, dyspnea, paresthesia, and urticaria.
Management in case of accidental poisoning:
symptomatic treatment and supervision in specialized care unit with fluid replacement and hypertensive treatment if necessary. Although there are no data available, it seems advisable to avoid the use of GABA agonists in the treatment of accidental intoxications due to ivermectin.

STORAGE CONDITIONS
Store at below 30°C.

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Manufactured By Neel Nayan Pharma Pvt. Ltd ., India
For
Benta SAL, Lebanon

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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