NAWAZAN PLUS BOLUS

(Levamisole HCl, Oxyclozanide, Cobalt Sulphate, Sodium Selenite)

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

NAWAZAN PLUS BOLUS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Bolus Contains:
Levamisole HCl …….. 1.125gm
Oxyclozanide …….. 2.250gm
Cobalt Sulphate ……... 0.286gm
Sodium Selenite …….. 0.026gm

3. PHARMACEUTICAL FORM

Bolus.

4. CLINICAL INFORMATION

4.1. Target species

Cattle, Sheep & Goat.

4.2. Indications for use specifying the target species

For the treatment and prevention of chronic fasciolosis and paramphistomatosis, gastro-intestinal and pulmonary nematode infections in cattle, sheep and goats. Eliminates mature and developing immature forms of nematode species.
The product is effective against the following parasites: Virtually eliminates all flukes (Fasciola spp.) found in the bile ducts of the liver. Destroys adult forms of Paramphistomatomum spp.; In the rennet: Haemonchus, Ostertagia and Trichostrongylus spp.; In the intestines: Trichostrongylus, Cooperia, Nematodirus, Oesphagostomum, Chabertia and Bunostomum spp.; In the lungs: Dictyocaulus spp.;

It is effective against immature and adult *Ostertagia* and in the treatment of Type II Ostertagiasis in cattle; it is not effective against inhibited larvae of *Ostertagia* (Pre-Type II Ostertagiasis) in cattle, therefore, a later follow-up treatment may be necessary. In sheep it is usually effective against inhibited/immunized *Haemonchus* larvae, *Ostertagia* and *Trichostrongylus axei*. Levamisole is also used as an immunostimulant to increase immune defense in viral infections and chronic recurrent diseases. It is used as an effective alternative treatment in cases of developed resistance to other chemically unrelated anthelmintic products.

4.3 Contraindications

Do not use in combination with organophosphorus compounds, as well as their application 14 days before and after the application of Polivermin – L. At the same time, animals can

be treated simultaneously with organophosphorus dressings for the treatment of edema caused by larvae of flies of the type *Oestridae*, only if they contain one of the following substances: phosmet, fenthion, metriphonate. Do not apply together with phenothiazine metpiridine and procaine; in animals with severe kidney and liver damage; in severely exhausted animals. Do not use in case of hypersensitivity to the active substances.

4.4 Special precautions for use in each target species

There is none.

4.5 Special precautions for use

Special precautions for animals when using the product

Not applicable.

Special precautions to be taken by the person administering the veterinary medicinal product to animals the animals

People with known hypersensitivity to levamisole hydrochloride and/or oxyclozanide should avoid contact with the veterinary medicinal product and administer the veterinary medicinal product with caution.

4.6. Adverse reactions (frequency and seriousness)

Very rare. Very rarely, at normal dose levels of oxyclozanide, slight softening of the faeces and transient loss of appetite may be observed in cattle. No adverse reactions have been observed at normal dose levels of levamisole

4.7. Use during pregnancy and lactation or lay

Pregnancy: It can be used during pregnancy.

Lactation: Can be used during lactation.

4.8 Interaction with other veterinary medicinal products and other forms of interaction

Available data indicate that this veterinary medicinal product cannot be administered together with organophosphorus compounds and diethylcarbamazine, with the phenothiazine metpyiridine and procaine.

4.9 Dosage and administration

It is administered orally, directly and individually for each animal in a dose: 1 bolus per 150 kg body weight, which corresponds to oxyclozanide 15 mg/kg body weight and levamisole hydrochloride 7.5 mg/kg body weight.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Overdose may cause sluggishness, some softening of the faeces in sheep and possibly diarrhoea, loss of appetite, head shaking, slight muscle tremors and weight loss in cattle. These symptoms are more pronounced in animals with severe liver damage and/ or dehydration at the time of treatment. Atropine may be used as an antidote if necessary.

4.11 Withdrawal period.

Meat and internal organs (offal) – 28 days.
Animals intended for human consumption must not be slaughtered during treatment.
Animals can be slaughtered for human consumption 28 days after the last treatment.
Not authorised for use in animals producing milk for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Oxyclozanide Pharmacotherapeutic group: anthelmintic agent. Veterinary Anatomical-Therapeutic Code: QP52AG06
Levamisole hydrochloride Pharmacotherapeutic group: anthelmintic. Veterinary Anatomical Therapeutic Code: QP52AE01

5.1 Pharmacodynamic properties:

Oxyclozanide

Oxyclozanide has a pronounced effect against the large liver fluke and paramphistoma. It affects adult (over 12 weeks) forms of *Fasciola hepatica* and *Fasciola gigantica* and less effectively young forms of *Fasciola hepatica*.

Oxyclozanide is an anthelmintic of the salicylanilide group. The mechanism of action of oxyclozanide is the uncoupling of oxidative phosphorylation in the methyl group. It may act in more than one way to reduce ATP levels, leading to metabolic dysfunction and death of the parasites. There is no evidence of secondary pharmacodynamic effects.

Levamisole hydrochloride

Levamisole is a levorotatory isomer of tetramizole from the group of imidazothiazoles. It has a pronounced anthelmintic activity against nematodes parasitic in the gastrointestinal tract and respiratory tract of cattle, sheep and pigs. It is active against larvae, young and adult forms of nematodes, without affecting eggs. It is equally active when administered orally and parenterally. It causes paralysis of parasites by disrupting energy metabolism (inhibition of the activity of fumarate reductase in mitochondria and the conversion of fumaric acid to succinic acid - the tricarboxylic acid cycle, respectively the production of ATP, is interrupted) and by interrupting neuromuscular conduction (cholinergic effect, followed by persistent depolarization of postsynaptic membranes). Helps restore the suppressed immunological reactivity of the macroorganism (by activating T-lymphocytes and macrophage function) and induces the synthesis of interferon. It is not active against trematodes, cestodes, protozoa, bacteria and fungi. It is used for the treatment of gastrointestinal and pulmonary nematodosis in cattle and sheep (caused by the genera *Haemonchus, Ostertagia, Trichostrongylus, Marshallagia, Cooperia, Nematodirus, Chabertia, Strongyloides, Oesophagostomum, Bunostomum, Protostrongylus, Neascaris, Dictyocaulus, Gaigeria, Trichuris, Oskitagia, Mecistorrus)*, pigs (*Oesophagostomum, Metastrongylus, Strongyloides, Ascaris, Hyostrongylus, Trichuris)*, birds (*Ascarida, Capillaria, Heterakis, Syngamus, Amidostomum)*. Adult forms of the parasites are more sensitive than larvae and their young forms.

Cobalt sulphate are diverse and can manifest through various mechanisms. Primarily, cobalt is known to be an essential trace element, particularly for ruminants where it is crucial for the synthesis of Vitamin B12 by rumen microbes; Vitamin B12 is vital for various metabolic processes. However, beyond its essential role, higher exposures to cobalt sulphate can lead to adverse effects. It can disrupt cellular energy metabolism by uncoupling oxidative phosphorylation and inhibiting key enzymes, potentially leading to

the formation of cytotoxic reactive oxygen species and oxidative stress. Cobalt also has implications for erythropoiesis, with some suggestions of increasing erythropoietin (EPO) concentrations, though studies in horses have not always shown a direct effect on EPO or red blood cell parameters after a single administration. Furthermore, chronic exposure to cobalt, especially through inhalation, has been linked to respiratory irritation, allergic sensitization (including asthma and dermatitis), and more severe conditions like "hard metal pneumoconiosis" and cardiomyopathy. It is also classified as a suspected human carcinogen and has been associated with reproductive toxicity in animal studies.

Sodium selenite are largely attributed to its role as a source of selenium, an essential trace element vital for various physiological processes. A key aspect of its action is its incorporation into selenoproteins, particularly glutathione peroxidases (GPx), which are crucial antioxidant enzymes. These enzymes protect cells from oxidative damage by neutralizing reactive oxygen species. Therefore, sodium selenite contributes to maintaining cellular integrity and function. Beyond its antioxidant role, sodium selenite, particularly at higher concentrations, can exhibit pro-oxidant effects. This is thought to occur through the generation of superoxide radicals and the depletion of cellular glutathione, which can lead to selective cytotoxicity in certain cell types, a mechanism relevant to its potential anti-cancer properties. Additionally, selenium plays a role in immune function, thyroid hormone metabolism, and reproductive health, with sodium selenite contributing to these processes by providing the necessary selenium substrate for the synthesis of relevant selenoproteins.

5.2 Pharmacokinetic properties

Oxyclozanide

Oxyclozanide is absorbed slowly after oral administration with peak plasma levels 24 hours after dosing. Excretion is primarily faecal. Lesser excretion occurs via the urine. A sulphone metabolite, two different glucuronides and the parent compound have been identified in the urine of some experimental animals. In the faeces the only component identified is the parent compound. The same metabolites, with the exception of the sulphone, are identified in the urine and faeces of sheep. In *in vitro* experiments, oxyclozanide is poorly or not metabolised in sheep liver microsomal suspension and only slightly metabolised in bovine liver microsomal suspension.

Levamisole hydrochloride

Levamisole is rapidly absorbed from the digestive tract and from the injection site, penetrates into all organs, tissues and fluids, and is excreted exclusively with urine and feces and to a lesser extent with milk. It is also excreted with tear secretion, which explains its activity against the eye nematode *Thlazia rhodesii*.

Cobalt sulphate, upon administration, can be absorbed through various routes, including ingestion, inhalation, and dermal exposure. The extent of its intestinal absorption varies with the dose, with iron transport mechanisms in the small intestine potentially influencing its uptake. Once absorbed, cobalt distributes widely throughout the body, with a large volume of distribution and a normal body burden of approximately 1.1 mg. In ruminants, a notable metabolic pathway involves its conversion to Vitamin B12 by rumen bacteria. At a cellular level, cobalt can induce oxidative stress, reduce glutathione, and inhibit enzyme synthesis. The primary route of excretion for absorbed cobalt is through urine, with a smaller amount eliminated via bile. While initial urinary elimination is rapid, a slower phase can persist for several weeks, and cobalt serum concentrations can remain elevated for extended periods due to a prolonged gamma half-life.

Sodium selenite, when administered, is rapidly absorbed from the digestive tract and injection sites. Its oral bioavailability can vary, sometimes showing a logarithmic inverse relationship with the dose. Once in the systemic circulation, sodium selenite quickly distributes into plasma, tissues, and various bodily fluids, with its distribution and accumulation varying among different organs. The kinetics of its distribution in plasma, liver, and kidney often follow a two-compartment open model, while other tissues like the heart and muscle may fit a one-compartment model. Metabolically, sodium selenite can be incorporated into selenoproteins, which have antioxidant functions, but it can also deplete glutathione and generate reactive oxygen species. Elimination predominantly occurs via urine and feces, with some excretion also observed in milk and tear secretion. While urinary excretion is a major route, a portion of selenium may not be fully excreted, suggesting some accumulation or volatile excretion pathways.

Environmental impact
There are no known data on harmful effects on the environment.

6. PHARMACEUTICAL INFORMATION

6.1 Incompatibilities

In the absence of compatibility data, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.2. Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the container: use immediately in 28 days, do not store.

6.3. Special precautions for storage

Do not store below 25°C.
Store in a dry place
Protect from light and moisture.
Keep out of the reach of children.
To be used as directed by the registered veterinary practitioner only.

6.4. Nature and composition of primary conditioning

30's & 10's Alu/PVC blister in Unit carton

SPECIAL PRECAUTIONS FOR THE DISPOSAL OF WASTE MATERIALS
UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS

Any unused veterinary medicinal products or waste materials derived from such medicinal products should be disposed of in accordance with local requirements and placed in appropriate collection and disposal systems for unused or expired medicinal products.

7. MARKETING AUTHORISATION HOLDER

Nawan Laboratories (Pvt.) Ltd.
Plots No. 136-138, Sector-15,
Korangi Industrial Area, Karachi-74900, Pakistan.

8. MARKETING AUTHORISATION NUMBER

Reg. No. 035064

9. DATE OF FIRST AUTHORISATION

Date of Reg.: 14.12.2004

10. DATE OF REVISION OF THE TEXT

10-07-2025

MANUFACTURED BY:

NAWAN LABORATORIES (PVT) LTD.

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