APPROVED BY
Deputy Head of
Rosselkhoznadzor
N.A. Vlasov
18 of May 2015

DIRECTION FOR USE
of the preparation Endoviraza®
for prophylaxis and treatment of viral respiratory diseases of calves, colts, chickens, and viral diseases of bees.
(Organization–originator: "Severniy stil" Ltd., Moscow)

I. General information

1. Trade name of the medicinal product: Endoviraza®.
International nonproprietary name: Bacterial endonuclease.

2. Formulation: lyophilisate for preparation of solution for outward, intranasal, and inhalation application.

The Endoviraza® contains bacterial endonuclease (deoxyribonucleate (ribonucleate) 5'- nucleotide hydrolase) enzyme as an active ingredient and magnesium sulphate as an enzyme activator. The product is manufactured as a kit. One kit contains a vial with 10 mg of endonuclease with an activity of 10 000 units or a vial with 50 mg of endonuclease with an activity of 50 000 units and the corresponding vial with 0.12 or 0.62 g of magnesium sulphate. Also the flask with endonuclease contains polyglucin (polysaccharide dextran) of 9 mg or 45 mg as excipients, respectively.

3. It is manufactured as a kit consisting of 2 glass vials. The first vial contains the Endoviraza® in the quantity of 19 mg with an activity of 10 000 units or 95 mg with an activity of 50 000 units. The second vial contains magnesium sulphate in the quantity of 0.12 g or 0.62 g, respectively. Both vials are corked with rubber stoppers fixed with aluminium caps and packed into a package or into a cardboard box with the direction for use.

3. The shelf-life of the Endoviraza® is 4 years from the date of manufacture, if stored under the recommended conditions. The Endoviraza® should not be used after the expiration date.

4. The Endoviraza® should be stored as an unopened original package in a dry place away from direct sunlight, separately from food products and feed at a temperature from 0°C to 25°C.

5. The Endoviraza® should be stored out of reach of children.

6. The unused product should be disposed in accordance with the requirements of legislation.

II. Pharmacological properties.

7. The Endoviraza® is classified among the antiviral product group of microbiological origin. It exhibits apparent antiviral characteristics, namely it suppresses multiplication of various viruses by hydrolysis of nucleic acids. In the case of intranasal and inhalation application, endonuclease is subject to adhesion. It penetrates deeply into mucous membranes of respiratory passages where it affects viruses of animal respiratory diseases. A negligible amount is absorbed into blood where it is transformed and excreted by urinary way. In the case of spraying of bees, the product penetrates through bee integument into hemolymph and is transferred over the whole organism causing virus inactivation.

The Endoviraza® is classified as a low-hazardous substance (substance hazard category 4 according to the GOST 12.1.007-76) in terms of an effect on organisms. The product does not have any local irritant and sensitizing effect. The Endoviraza® is non-toxic for bees. The product, if applied in recommended doses, does not have any negative effect on overall condition of bees. It stimulates the development and productivity of bee families.

III. Application procedure

8. The Endoviraza® is used for prophylaxis and treatment of viral respiratory diseases of calves and colts (infectious rhinotracheitis, respiratory syncitial viral infection, adenoviruses of 1 and 2 types, etc.), chickens (infectious laryngotracheitis of poultry, bronchitis of poultry, Newcastle disease), bees (acute bee paralysis and chronic bee paralysis, filamentovirosis, sacbrood disease, egyptovirosis, etc.) and for spring-summer stimulation of the development of bee families.

9. The contraindications for product application are oversensitivity of individual animals towards product components.

10. The Endoviraza® is used for inhalation in the form of aerosol or intranasal and outward applications are appropriate as well.

The Endoviraza® in the quantity of 50 000 activity units (the content of one vial) should be dissolved at a room temperature in 150 ml of boiled water. 0.62 g of magnesium sulphate (the content of second vial) should be added into this solution. The Endoviraza® in the quantity of 10 000 activity units (the content of one vial) should be dissolved at a room temperature in 30 ml of boiled water. 0.12 g of magnesium sulphate (the content of second vial) should be added into this solution. This solution is valid for 24 hours at a room temperature.

For treatment of respiratory diseases, the solution of the product should be administered into calves or colts in the volume of 2.5 ml into each nostril of nasal passages in the form of a drop-size spray using a spray machine enabling to dispense the prepared solution. A dose for one calf (colt) is approximately 1 600 activity units. The prepared solution from a vial with an activity of 10 000 units is sufficient for one-time treatment of 6 heads, and the solution with an activity of 50 000 units is sufficient for one-time treatment of 30 heads. Treatment is implemented once a day, 4-5 times with an interval of 1-3 days. For prophylactic purposes calves (colts) of 0.5-2-months-old should be treated by intranasal route, 2

times with an interval of 7-10 days.

For prophylaxis and treatment of virus diseases in chickens, the Endoviraza® in the quantity of 50 000 activity units (the content of one vial) should be dissolved at a room temperature in 500 ml of boiled water. 0.62 g of magnesium sulphate (the content of second vial) should be added into this solution. The Endoviraza® in the quantity of 10 000 activity units (the content of one vial) should be dissolved at a room temperature in 100 ml of boiled water. 0.12 g of magnesium sulphate (the content of second vial) should be added into this solution. The work solution is used assuming 15 ml for 1 m^2 of a poultry yard if floor-managed. The work solution is used assuming 15 ml for 1 m^2 of a floor cage area if cage-managed or for 0.5 m^3. This solution is valid for 24 hours at a room temperature.

The product is applied in the form of finely-divided aerosol using a generator of cold fog, aerosol generators of SAG type, etc. The recommended length of the blow-off body is 5 -10 meters and the height of the spraying level should be at least 40 sm above the ground. The size of sprayable particles is from 5 to 15 microns. For household plots there can be used manual mechanical finely-divided aerosol sprayers ("Rosinka"-type, reciprocating spray machines, trigger fixtures, etc.). The recommended age of chickens for vaccination with the Endoviraza® product against viral respiratory diseases is 19-35 days under commercial-scale conditions. If vaccination was absent, chickens are recommended to be treated since their first days: 3-4 times with intervals of 3-4 days.

For treatment of virus diseases, bees should be treated in a spring-summer period at an air temperature above 14°C up to 7 times if needed with intervals of 7-10 days. For 2 bee families, the Endoviraza® in the quantity of 10 000 activity units (the content of one vial) should be dissolved at a room temperature in 100 ml of boiled water. 0.12 g of magnesium sulphate (the content of second vial) should be added into this solution. For 10 bee families, the Endoviraza® in the quantity of 50 000 activity units (the content of one vial) should be dissolved at a room temperature in 500 ml of boiled water. 0.62 g of magnesium sulphate (the content of second vial) should be added into this solution.

For prophylaxis and stimulation of the development of bee families, bees should be treated at least 3 times with intervals of 7-10 days. For better over-wintering of diseased families, they should be once treated at the end of the beekeeping season before family gathering.

The bee families are treated with the solution of the Endoviraza® in the morning (before bee flight) or in the evening (after bee flight) with the use of a mechanical finely-divided aerosol sprayer ("Rosinka"-type, spray painting machine "Blesk", etc.).

Each beeway should be sprayed with a dose of 4-5 ml for 2-3 seconds. Consumption of the product solution for one bee family with power of 10-12 standard frames is 40-50 ml (5000 activity units).

11. The overdose symptoms are not established as a result of product application.

12. The peculiarities of action of the product as a result of its first application or its dechallenge are not established.

13. If the recommended repeated treatment schedule is failed, usage of the product should be restarted according the same scheme and dosage.

14. If the Endoviraza® is used according to the present direction for use, as a rule there should not be any side effects or complications.

15. There is no data about incompatibilities of the product with other medicinal drugs and supplementary feed. Application of the Endoviraza® does not preclude the use of specific therapy products and implementation of medical and preventive actions for animal infectious diseases including poultry specified in appropriate directions for use.

16. The products obtained from animals treated with the Endoviraza® according to the present direction for use can be used without any restrictions.

IV. Individual preventive measures.

17. At working with the Endoviraza®, it is necessary to follow the common rules of personal hygiene and safety rules prevailing when operated with medicinal products. Rubber gloves and a respirator should be used as well.

18. While working, it is forbidden to smoke, drink and eat. After work wash thoroughly your face and hands with soap. If the medicinal product gets on skin or mucous membranes of eyes, it is recommended to wash the affected area with a large amount of water. Persons having hypersensitivity towards components of the product should avoid direct contact with the Endoviraza®. In the case of allergic reactions or accidental penetration of the product into human organism, person should seek medical attention and inform a doctor (keep the direction for use or the label to hands).

19. It is forbidden to use the empty product packages for domestic use. They should be disposed along with household waste.

20. Organization-manufacturer:

- “Trade company “BiAgro” Ltd., Russia, Vladimir, Lakina street, 4-B
- JSC “Pokrov biological plant”, Volginsky settlement, Petushinsky district, Vladimir region, Russia, 601125

The direction for use has been worked out by: “Severniy stil” Ltd., 109202, Moscow, shosse Frezer, 5/1, facility 1, room 46.

At the moment of approval of the present Direction, the direction for use of the Endoviraza® approved by Rosselkhoznadzor on the 09 of October 2014 becomes inoperative.

It is recommended for registration in the Russian Federation by FGBI “VGNKI".

The number of the Registration Certificate: 77-3-21.12-2619№PVR-3-4.9/00188.