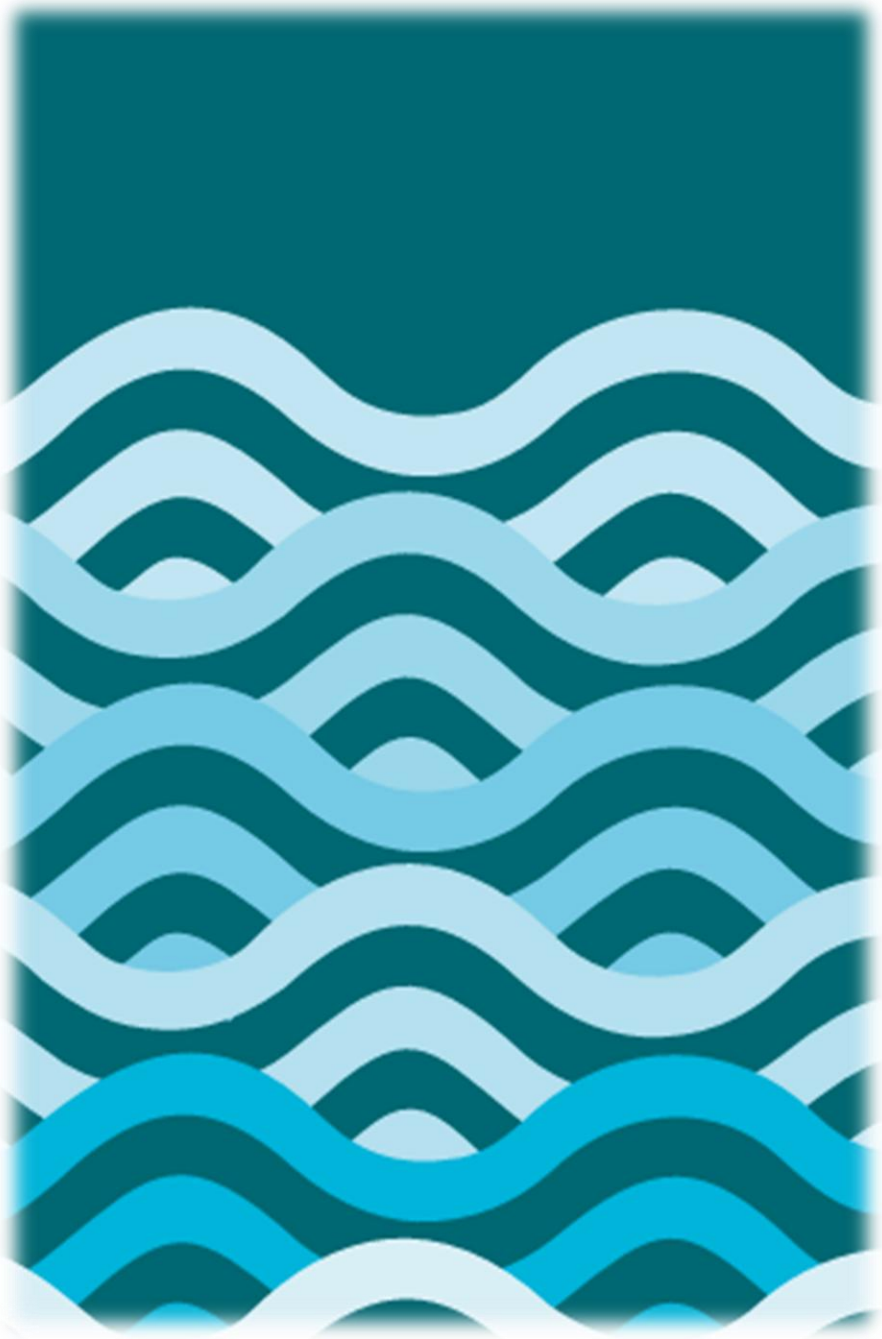


Vethellas

PRAZIVETIN®

Effective Protection for Gilthead Sea Bream against gill fluke infestations

1.Product Overview

PRAZIVETIN® is a medicated feed premix (50% Praziquantel); administered with the feed it constitutes an effective anthelmintic antiparasitic treatment for cage farmed gilthead sea bream (*Sparus aurata*). It targets monogenean ectoparasites, specifically *Sparicotyle chrysophrii*. As a feed based treatment, the use of PRAZIVETIN® against Sparicotylosis is not restricted from equipment/personnel/weather conditions, permitting the simultaneous treatment of several cages at the same time and at the appropriate time intervals in conformity with the biological cycle of the parasite, for an effective control of re-infections and parasite abundance in farmed gilthead sea bream stocks.

- **Active Substance**

Praziquantel

- **Target Animal Species**

Gilthead sea bream (*Sparus aurata*)

- **Therapeutic Indications**

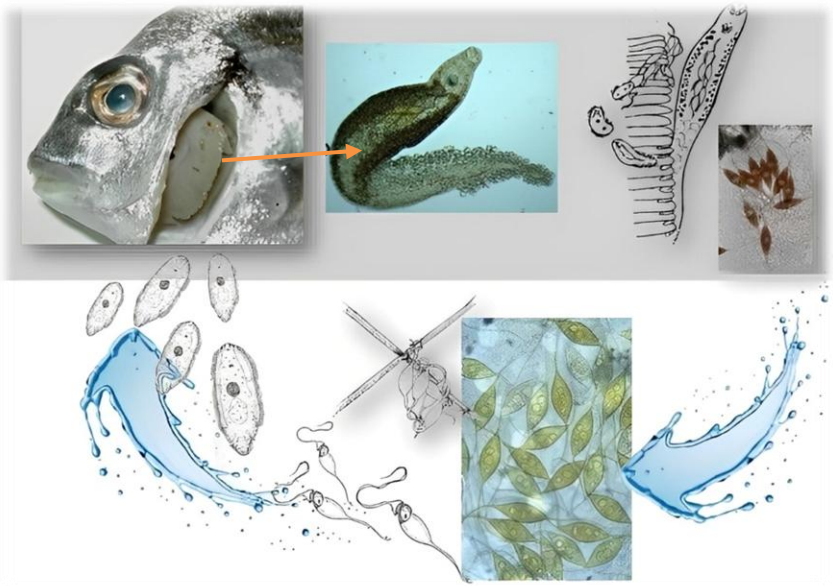
For the treatment and prevention of ectoparasitic infestations of the gills caused by the monogenean parasite *Sparicotyle chrysophrii* (disease: Sparicotylosis).

Gilthead seabream showing anemic gills due to infection with S. chrysophrii. Photo: Fish Pathology Lab, University of Bologna

2. The Problem – Sparicotylosis in Gilthead Sea Bream Farming

Gill parasitism of gilthead seabream by monogenean parasites of the species *Sparicotyle chrysophrii* has recently emerged as the most serious disease condition in the seabream farming sector throughout the Mediterranean, based on the economic impact on production compared to other diseases affecting the species.

Sparicotyle is highly infectious under intensive farming conditions (unit concentration, high stocking density, proximity of different age groups of fish, hindered water renewal due to net fouling, presence of wild carrier fish populations). It has a direct biological cycle and reproduces by laying eggs that are resistant to fish treatments either by bath or oral administration. The eggs have filaments that aid their attachment to submerged surfaces in the environment of the cage farm units (culture nets, cage components, mooring equipment, and seabed surfaces).



Life cycle of Sparicotyle chrysophrii
(Department of Veterinary Medical Sciences, University of Bologna, Italy, PerformFISH, 2020)

Each egg hatches into the infective larval stage of the parasite, the "oncomiracidium", which swims and has a limited lifespan to find gilthead seabream gills to attach to and develops into the immature and subsequently the mature form of the parasite. The juvenile and adult parasites are small blood-sucking worms a few millimeters in length that anchor themselves to the gill epithelium using their posterior attachment organ (the "opisthaptor") which is equipped with and array of clamps. With their action they cause lacerations in the gill epithelium, through which they insert their anterior end/snout (the "prohaptor"), where their mouth is and which is -equipped with buccal suckers and a muscular pharynx, and feed on blood.

Localization	Gills
Host	Highly specific to the host: Gilthead seabream (*Sparus aurata*) - Affects all life stages but juveniles are more susceptible
Impact	Varies depending on the intensity of infections and age (smaller fish, higher susceptibility). The disease causes reduced performance indicators and increased mortality in juveniles and predisposes to bacterial infections.
Factors contributing to disease outbreak	High stocking density, low water exchange, infrequent net changing
Trasmission	Horizontal

Overview of Gill Parasite Infection in Gilthead sea bream (*Sparus aurata*)

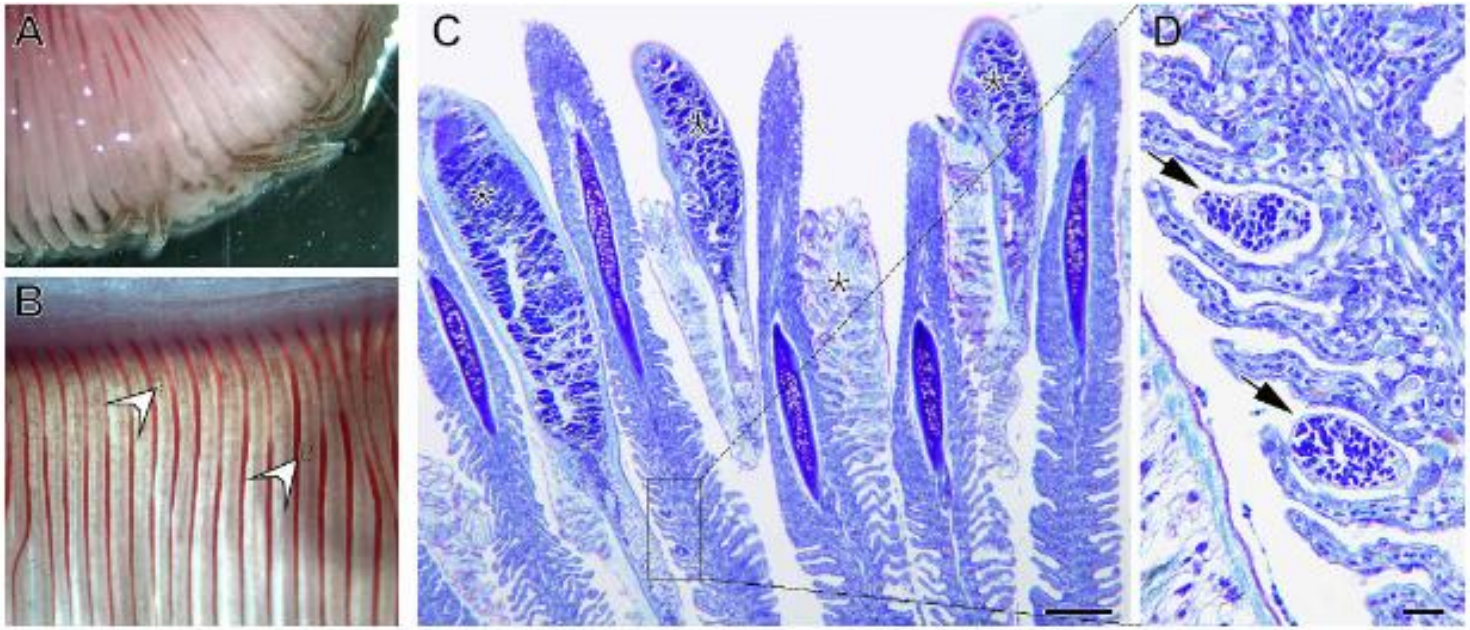
These parasitic infections, facilitated by the growth of the gilthead sea bream aquaculture sector and the inherent problem of farms lacking alternative sites (which would allow leaving a site fallow for a certain period), have become endemic in farmed seabream populations throughout the Mediterranean. **They result in heavy parasite burdens that cause:** reduced fish performance (slower growth, poorer feed conversion) due to the osmotic stress and the blood loss/anemia; breathing difficulties due to the anemia and gill epithelial lesions (necrosis, hyperplasia, excessive mucus secretion); internal organ damage (liver, myocardium); increased mortality (from the parasites themselves or secondary infections through gill lesions); and reduced product quality due to the anemic gills.

Adult Sparicotyle chrysophrii parasites and their eggs under the stereomicroscope (x10 magnification).

Seasonality

Problems from this parasitic infection begin when fish reach a size of 15–20 g, a few weeks after being stocked in the sea cages. The parasite infestation persists year-round, but the parasite load and the severity of the disease increase with the rise of the water temperature above 16°C and up to 26°C, due to the acceleration (shortening) of the parasite's life cycle - 56 days at 20°C - and increased hatchability rate.

Impact: Without treatment, mortality rates can reach up to 30–35% per farming cycle unless very low stocking densities are maintained, which might halve mortality — but either way, farming becomes uneconomical.



High-resolution images show *Sparicotyle chrysophrii* at various developmental stages affecting the gills. Adult parasites are found near the filament apices (A), while post-larvae and juveniles are close to the arch cartilage (B, white arrowheads). Histological analysis confirms the presence of adult parasites (C, asterisks) and highlights two juveniles in detail (D, black arrows). *Photo: Ferrer et al. (2023).*

3. The Solution – PRAZIVETIN® – Effective, Feed-Based Anthelmintic Treatment

Dosage

The recommended dosage of PRAZIVETIN® for treating *Sparicotyle* infestations in gilthead sea bream is 300 mg per kg of body weight (BW) (i.e., equivalent to 150 mg/kg BW of active substance) per day for 3 consecutive days, administered with the feed. The 3-day administration is considered necessary in order to maximize the likelihood that all fish in a cage receiving treatment get a uniform dose of the medicinal product, and to eliminate parasites from new infections on days 1 and 2 of the treatment.

Administration route

Oral, via medicated feed

Farm-Wide Parasite Load Control

- It is recommended that treatments be carried out simultaneously in all cages of a year class of gilthead sea bream juveniles. A repeat treatment is advised 1–5 weeks after the first, depending on the seasonal variation of the parasite's life cycle duration, in order to kill parasites that hatch from the resistant eggs after the first 3-day treatment and before they reach reproductive maturity. Adult parasites are hermaphroditic and produce around 20 eggs daily for as long as their reproductive life lasts (a few weeks).

Scientific works that studied the life cycle of the parasite recommend the following re-treatment intervals according to the water temperature:

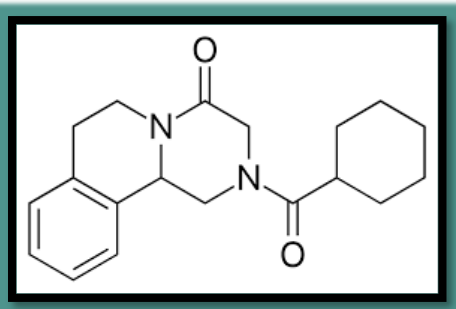
- 26°C: 8–14 days
- 22°C: 9–21 days
- 18°C: 11–28 days
- 14°C: 14–35 days

4. The active substance - Praziquantel

Mode of action

The active ingredient of the PRAZIVETIN®, i.e. praziquantel, is a synthetic broad-spectrum anthelmintic that has been extensively used in veterinary medicine for the treatment of helminthiasis in animals and in human medicine for the treatment of schistosomiasis (caused by digenean trematode blood parasites) for decades.

In farmed fish, it has been clinically proven effective against: monogenean worms parasitizing the gills and skin of various marine fish such as parasites of the genera *Zeuxapta*, *Microcotyle*, and other *Polyopisthocotylea*, the genus *Benedenia*, digenean trematode worms of the genus *Cardicola* parasitizing the heart cavities and blood vessels of bluefin tuna species (*Thunnus spp.*), larval stages of digenean trematode worms that are encysted in various organs (eyes, skin, muscles, brain), and intestinal parasitic cestodes (tapeworms) such as *Eubothrium* spp. that infects Atlantic salmon. In gilthead sea bream, PRAZIVETIN® has shown high efficacy against *Sparicotyle chrysophrii* (86-89% kill of young and mature parasites following a 3-day treatment).



In sea bream, PRAZIVETIN® has shown high efficacy against Sparicotyle (86-89% mortality of young and mature parasites after a 3-day treatment).

Pharmacodynamics

Praziquantel acts by causing intense spasms and paralysis of the muscles in the worms. This paralysis is accompanied by — and is possibly caused by — rapid influx of Ca^{2+} into the interior of the parasite. Morphological lesions are another early effect of praziquantel. These lesions are accompanied by increased antigen exposure on the surface of the parasite. Calcium ion channels in flatworms are currently the only known target of praziquantel.

Pharmacokinetics

After oral administration, praziquantel is rapidly absorbed by the intestinal mucosa of the fish, enters the bloodstream, and diffuse to various tissues in the body, including the blood plasma and gills.

The bioavailability of praziquantel in gilthead sea bream after oral administration with the feed was found to be around 49%, partly limited by first-pass metabolism, which, however, is not as pronounced as in terrestrial livestock.

At the recommended oral dose of 150 mg/kg body weight, praziquantel reaches a maximum concentration of 8.2 µg/mL in the blood plasma at 6 hours, while in the gill tissue, the maximum concentration reaches 39.1 µg/g at 4 hours. The active substance is then largely metabolized within 24 hours of oral administration, with a half-life of 14.1 hours, calculated in the blood plasma of the sea bream at a water temperature of 21°C.

5. Medicated Feed Preparation

Preparation Instructions

Medicated fish feed containing the veterinary medicinal product must be prepared based on a veterinary prescription and only by approved manufacturers licensed to produce medicated fish feeds.

Recommended Method of Incorporation into Feed

PRAZIVETIN® may be incorporated via:

a) Surface coating of previously produced extruded feed pellets by mixing them with the product, adding fish oil for adhesion/adsorption, and using appropriate drum mixer equipment.

or

b) Surface coating by mixing the product with fish oil and spraying the oily mixture onto pre-made extruded pellets (preferably under vacuum).

Recommended inclusion rate of PRAZIVETIN® into feed: 5–40 kg per ton of feed, depending on the feeding rate.
Recommended fish oil addition (also serves as an appetite enhancer): 30–50 L per ton of feed.
Recommended mixing time: 10–15 minutes.

6. Feeding Rate & Dosage Chart

The incorporation rate depends on the feeding rate, which varies with fish size and water temperature. Adjust the incorporation rate according to the following table:

Feeding rate (% BW/day)	Fish oil inclusion (%)	PRAZIVETIN® content in the medicated feed (kg/ton of feed)	Praziquantel content in the medicated feed (mg/kg of feed)	Fish biomass treated (kg/day/ton of feed)
0.75	4–5%	40	20,000	133,333
1.00	3–4%	30	15,000	100,000
1.25	3%	24	12,000	80,000
1.50	3%	20	10,000	66,667
1.75	3%	17.14	8,570	57,133
2.00	3%	15	7,500	50,000

Note: Accurate fish weight estimation is essential to avoid underdosing and development of resistance.

****Note: The fish feed should be representative of the feed used for the target species and the age of the fish that will undergo treatment. The composition of the final medicated feed, after the incorporation of the veterinary medicinal product, should not differ significantly from the typical recommended composition for the species.***

Special guidelines for ensuring a successful administration of the medication

Feeding:

- A 1-day fasting period is recommended to precede the start of treatment.
- During treatment, only medicated feed is recommended to be given in a single daily meal.
- Administer the medicated feed at a reduced feeding rate compared to the recommended rate. For example, if the recommended feeding rate for non-medicated feed is 2% of the fish body weight per day, administer the medicated feed at a rate of 1.0–1.25% of the fish body weight per day.

Pellet size:

- The medicated feed should be produced in pellet sizes smaller than those typically recommended for the size of the fish, in order to ensure that even smaller fish in the population can consume it, and so that the fish swallow the feed as whole as possible thus reducing losses due to chewing and preventing the taste of the active ingredient brought up which may cause loss of appetite and reduced medicated feed intake.
- For a specific range of fish sizes, it is recommended to use pellets one size smaller than those recommended by the manufacturer for non-medicated feeds. Studies have found that, for fish weighing between 28 g and 215 g the smallest loss of feed from chewing is achieved with the use of pellets sized 2–2.5 mm.

Optimizing Fish Feed: The Importance of Pellet Size

Fish Health Condition – Parasitic Load:

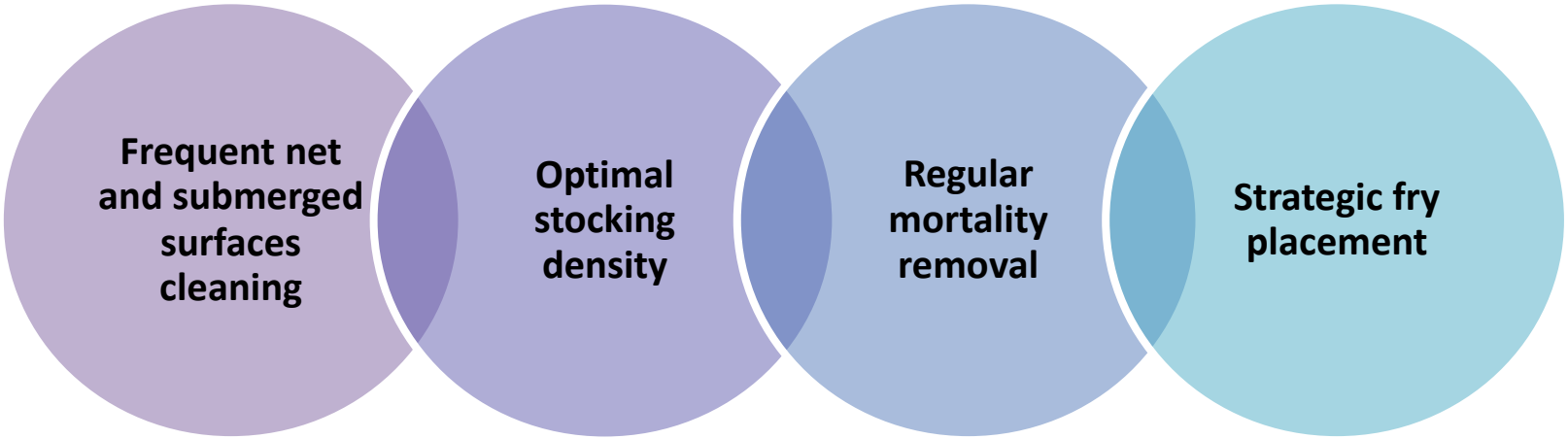
- It is important that the fish are not in an advanced stage of anemia/weakness when the treatment begins, as this could reduce their intake of medicated feed.
- Attention: The parasitic load level set as a criterion for any therapeutic intervention against *Sparicotyle* should be proportionally lower for smaller fish sizes, as smaller fish have less amount of blood, and the same number of parasites per fish will cause anemia much faster in smaller fish than in larger fish. For reference, the blood consumption by *Sparicotyle* parasites has been found to range at 4.31 μL (microliters)/24 hours/parasite.

Recommended Additional Measures in Combination with Therapeutic Interventions Against the Parasite:

For effective disease control, it is crucial that therapeutic interventions against the parasite are accompanied by good husbandry practices aiming at reducing the prevalence and spread of the parasite in the farming unit, such as:

- Frequent net changes and periodic cleaning of other substrates where parasite eggs may attach (e.g., submerged parts of the mooring system: ropes, fish cage pipes, buoys, etc.).
- Implementation of proper stocking densities without exceeding the limits stipulated by the farm's permit.
- Frequent collection and removal of mortality from fish cages.
- Placement of newly introduced batches of fry at the beginning of the floating unit of cages in the direction of the usually prevailing currents and, if possible, in cages that are somewhat distanced from those with the larger fish.

Combine with good husbandry practices such as:



7. Other information

Environmental safety

Based on ecotoxicological studies and studies on the environmental degradation of the active substance in the cage farm environment, it has been determined that the risk to the environment from using this veterinary medicinal product in the recommended manner for this specific indication does not exceed acceptable levels.

Contraindications/Side Effects

No adverse effects have been found to occur at the recommended dosage.

Overdose may cause temporary reduction of feed intake. Increased ALT/SGPT activity has been reported at five times the recommended dose, indicating possible liver toxicity.

Withdrawal Time for Sea Bream

120 degree-days

NB: For off-label use in other fish species for other helminthiasis indications, the dosage may differ – consult your veterinarian; warning: in such cases, a withdrawal time at least one and a half times longer than the above must be followed, in accordance with the applicable legislation (EU Reg. 2019/6, Article 115d(i)).

Packaging, Storage

Low-density polyethylene (LDPE) bags of 2 kg, available in a cardboard box containing 8 bags.

Low-density polyethylene (LDPE) bag of 20 kg, available in a three-ply paper bag with an internal polyethylene (PE) lining.

Store the bags tightly closed to protect them from moisture.

This medicinal product does not require special temperature conditions for storage.

Shelf-Life

Shelf life of the veterinary medicinal product according to the sale package: 2 years.

Shelf life after opening the primary packaging: 3 months.

Shelf life after incorporation into animal feed pellets according to the instructions: 3 months.

Marketing authorisation number(s)

EU/2/25/340/001–002

8. Contact & Distribution

Marketing authorisation holder, manufacturer responsible for batch release and contact details to report suspected adverse reactions

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