1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Kexxtone Veterinary

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Monensin 32.4 g (equivalent to 35.2 g monensin sodium)

Each intraruminal device contains 12 subunits each containing 2.7 g monensin (equivalent to 2.9 g monensin sodium).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Continuous-release intraruminal device.

A cylindrical orange polypropylene intraruminal device uniquely identified with a number, fitted with wings, consisting of a core which presents as a stack of 12 subunits.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (dairy cows and heifers)

4.2 Indications for use, specifying the target species

For the reduction in the incidence of ketosis in the peri-parturient dairy cow/heifer which is expected to develop ketosis.

4.3 Contraindications

Do not use in animals weighing less than 300 kg bodyweight.

Do not use in cases of hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings for each target species

Identification of animals for treatment should be at veterinary discretion. Risk factors may include a history of energy-deficiency-related diseases, high body condition score and parity.

In the event of early regurgitation, identify the animal by matching the animal ID number with the number on the intraruminal device and re-administer an undamaged intraruminal device (See section 4.5).

4.5 Special precautions for use

Special precautions for use in animals

Hold treated cattle in a confined area for 1 hour after administration to observe for failure to swallow or regurgitation. If this occurs re-administer the intraruminal device if undamaged. If damaged, administer a new intraruminal device. Recheck cattle for up to 4 days after dosing to observe for signs of an intraruminal device lodging in the oesophagus.

Signs of lodging may include bloat which may be followed by coughing, drooling, inappetence and unthriftiness.

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

Exposure to the active substance may elicit an allergic response in susceptible individuals.

People with known hypersensitivity to monensin or any of the excipients should avoid contact with the veterinary medicinal product.

Do not eat, drink or smoke when handling the veterinary medicinal product.

Use gloves when handling an intraruminal device, including during retrieval of a regurgitated intraruminal device.

Remove gloves and wash hands and exposed skin after handling intraruminal devices.

Other precautions

Ingestion or oral exposure to monensin can be fatal in dogs, horses, other equines or guinea fowl. Do not allow dogs, horses, other equines or guinea fowl access to veterinary medicinal products containing monensin.
Due to the risk of bolus regurgitation, do not allow these species access to areas where treated cattle have been kept.
Keep dogs away from treated animals. Accidental ingestion of active ingredient by dogs has resulted in fatal consequences. In case of suspected ingestion by dogs, seek veterinary advice immediately.

4.6 Adverse reactions (frequency and seriousness)

In rare cases, digestive signs (e.g. diarrhoea, ruminant stomach disorder) have been observed.
In very rare cases, oesophagus obstruction has been observed.
The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medical product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.7 Use during pregnancy, lactation or lay

Canbe used during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interaction

None known.

4.9 Amounts to be administered and administration route

Intraruminal use.
A single intraruminal device is to be administered to a dairy cow/heifer 3-4 weeks prior to expected calving, using an appropriate administration tool.
Kexxtone Veterinary delivers an approximate average dose of 335 mg of monensin per day for approximately 95 days.
Follow instructions carefully.
Adequate animal restraint is required to properly administer this intraruminal device. Such restraint must limit forward/backward motion and allow the animal's head to be held in the forward extended position and without pressure on the neck to prevent choking.
1. Each intraruminal device has an individual number along the device body. This should be recorded with the corresponding animal identification number so that, should an intraruminal device be regurgitated, the animal can be identified.
2. Fold wings down along the intraruminal device body and insert the device into an appropriate administration tool, orifice end first.
3. Restrain the animal with its head and neck stretched forward. Grasp the animal with one hand in the corner of the animal's mouth. Introduce the administration tool into the mouth avoiding

the front teeth. In order to avoid trauma and damage to the pharynx and oesophagus, do not use excessive force.
4. Insert the administration tool past the base of the tongue making sure to avoid the molar teeth. As the animal swallows, the administration tool will move easily over the base of the tongue. DO NOT USE EXCESSIVE FORCE. If resistance is encountered, withdraw the tool slightly and repeat the procedure.
5. Be sure the head of the administration tool is past the base of the tongue. When the animal swallows, eject the intraruminal device from the administration tool.

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

Accidental administration of more than one intraruminal device could result in some adverse reactions which are typical of monensin overdose, including decreased appetite, scouring and lethargy. These are generally transient. The highest tolerated dose is typically between 1 mg and 2 mg monensin/kg bodyweight/day.

4.11 Withdrawal period(s)

Meat and offal: zero days
Milk: zero days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other alimentary tract and metabolism products: drugs for prevention and/or treatment of acetonemia. ATC vet code: QA16QA06
Monensin is a member of the pharmacotherapeutic group of polyether ionophores, specifically the carboxylic subgroup. They are the product of natural fermentation products produced by *Streptomyces cinnamonensis*.

5.1 Pharmacodynamic properties

Monensin binds to bacterial cell membranes and interferes with the maintenance of important ion gradients in the cell which are needed for the transport of nutrients and to generate proton-motive force. Monensin is mainly active against Gram-positive bacteria. Gram-negative bacteria have complex outer cell membranes, resulting in inherent resistance to the action of ionophores. Thus, the ultimate effect of monensin within the rumen is to shift the microbial population resulting in a decrease of the bacteria that produce acetate and butyrate and increasing the bacteria that produce propionate, the gluconeogenic precursor. As a result of the change in population of bacteria within the rumen, efficiency of energy metabolism is improved. In the peri-parturient dairy cow, the positive effects of monensin include reduced blood ketones, increased serum glucose and reduced incidence of ketosis.

5.2 Pharmacokinetic particulars

The site of action for intraruminal administered monensin is the gastrointestinal tract.
Intraruminal administration of monensin is followed by extensive first pass metabolism which results in low concentrations of monensin in the systemic circulation. Metabolites and parent drug are excreted in the bile.
When the tablet-subunits inside the intraruminal device are in contact with rumen fluid at the orifice of the device, a gel is formed and is slowly released from the intraruminal device. Monensin is released from the intraruminal device at an approximate average dose of 335 mg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<u>Subunit</u>
Sucrose fatty acid ester

Carbomer
Lactose monohydrate
Magnesium stearate
Silica, colloidal anhydrous
Device
Polypropylene* orifice cap.
Polypropylene* plunger.
Polypropylene* barrel and wing.
Steel spring.
*The polypropylene components are coloured with sunset yellow E110

6.2 Major incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Shelf life after first opening the immediate packaging: 6 months

6.4. Special precautions for storage

Keep the foil tightly closed.

6.5 Nature and composition of immediate packaging

Aluminium foil bag containing 1 or 5 intraruminal device(s).
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product, waste materials derived from such veterinary medicinal products or regurgitated intraruminal devices should be disposed of As toxic waste, do not throw to sewer.

7. MARKETING AUTHORISATION HOLDER

Euromar Ltd.
P.O.B. 1064
Ramat Hasharon
Israel

8. MARKETING AUTHORISATION NUMBER(S)

153 39 34006

Revised on August 2021 according to MOH guidelines