[Version 9,03/2022]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Dobroxine 500 mg/g + 50 mg/g powder for use in drinking water/milk for calves

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g contains:

Active substances:

Doxycycline	500.0 mg
(as doxycycline hyclate	596.0 mg)
Bromhexine hydrochloride	50.0 mg

Excipients:

Qualitative composition of excipients and other constituents
Citric acid
Lactose monohydrate

Light yellow powder.

3. CLINICAL INFORMATION

3.1 Target species

Cattle (pre-ruminant calves).

3.2 Indications for use for each target species

Cattle (pre-ruminant calves): Treatment of respiratory infections caused by *Pasteurella multocida* and *Mannheimia haemolytica*.

3.3 Contraindications

Do not use in cases of hypersensitivity to tetracyclines, to bromhexine or to any of the excipients.
Do not use in animals with hepatic dysfunction.
Do not use in animals with functional rumen.

3.4 Special warnings

As eradication of the target pathogens may not be achieved, medication should therefore be combined with good management practices, e.g. good hygiene, proper ventilation, no overstocking.

The use of the veterinary medicinal product in conditions other than those recommended in the Summary of Product Characteristics may increase the prevalence of bacteria resistant to doxycycline and decrease the efficacy of treatment with tetracyclines as a consequence of cross-resistance.
Avoid its administration in rusty drinkers.

3.5 Special precautions for use

This veterinary medicinal product does not contain any antimicrobial preservative.

Special precautions for safe use in the target species:

Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.

Use of the product should be in accordance with official, national and regional antimicrobial policies.

Narrow spectrum antibiotic therapy with a lower risk of antimicrobial resistance selection should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

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

- This veterinary medicinal product may cause hypersensitivity reactions (allergy). People with known hypersensitivity to tetracyclines or bromhexine should avoid contact with the veterinary medicinal product.
- This veterinary medicinal product may produce adverse effects or cause irritation to the skin, eyes and mucous membranes.
- Handle the veterinary medicinal product with care to avoid production of dust and inhalation of dust particles as well as contact with skin and eyes.
- Personal protective equipment consisting of impervious gloves, overalls, approved safety goggles and an appropriate dust mask (e.g. disposable half-mask respirator conforming to European Standard EN149 or a non-disposable respirator to European Standard EN140 with a filter to EN143) should be worn when handling the veterinary medicinal product.
- Do not smoke, eat or drink while handling the veterinary medicinal product.
- In case of contact, rinse eyes with plenty of clean water and skin with soap and water.
- If you develop symptoms following exposure such as skin rash, seek medical advice and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes, or difficulty in breathing are more serious symptoms and require urgent medical attention.
- Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle (pre-ruminant calves).

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Allergic reaction. Photosensitivity. [1] Digestive tract disorder.

[1] Due to a intestinal dysbiosis.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Not applicable.

3.8 Interaction with other medicinal products and other forms of interaction

The absorption of doxycycline can be reduced in the presence of high amounts of calcium, iron, magnesium or aluminum in the diet. Do not administer together with antacids, kaolin and iron preparations.

3.9 Administration routes and dosage

Administration in milk.

Cattle (pre-ruminant calves): 10 mg of doxycycline (hyclate) + 1 mg of bromhexine hydrochloride/kg bodyweight/day, for 4-5 consecutive days equivalent to 20 mg of the product/kg bodyweight/day,.

Taking into account the dose to administer and the number and weight of the animals, it is possible to calculate the exact daily amount of veterinary medicinal product.
To ensure a correct dosage, body weight should be determined as accurately as possible to avoid underdosing.
The use of suitably calibrated measuring equipment is recommended if part of the packs are used.

The concentration of the veterinary medicinal product per litre of milk replacer should be calculated according to the following formula:

$$\text{mg of veterinary medicinal product per litre of milk replacer} = \frac{\text{mg veterinary medicinal product/kg b.w./day x mean body weight (kg) of animals to be treated}}{\text{Mean daily milk replacer intake/animal (l)}}$$

Once reconstituted with milk replacer, the solution should be consumed within 6 hours.
The use of suitably calibrated weighing equipment is recommended if part of containers is used.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

Not described.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Cattle (pre-ruminant calves):
Meat and offal: 16 days
Not authorised for use in animals producing milk for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QJ01AA20

4.2 Pharmacodynamic

Doxycycline is a bacteriostatic antibacterial agent that acts by interfering the bacterial protein synthesis of susceptible species.

Doxycycline is a semisynthetic tetracycline derived from oxytetracycline that acts on the 30S ribosomal subunit of bacteria by reversible binding. This binding blocks the union between tRNA-aminoacyl (transfer RNA) and the complex of mRNA and ribosomes. This avoids the addition of new amino acids to the peptide chain; thus, it inhibits the protein synthesis.

It acts against gram-positive and gram-negative bacteria.

Its antibacterial spectrum includes *Pasteurella multocida* and *Mannheimia haemolytica.*

Critical concentrations (breakpoints) of sensitive (S) or resistance (R) in µg/ml of tetracycline against bacteria that are not streptococcus are the following: (Source: CLSI 2008)

	S	**I**	**R**
Bacteria different from streptococci	≤ 4	8	≥ 16

There are at least two resistance mechanisms to tetracyclines. The most important mechanism is due to a decrease in the intracellular accumulation of the drug. It is due to an elimination route by antibacterial efflux or due to an alteration in the transport, decreasing the tetracycline uptake dependent on energy from the outside of the cell. The alteration in the transport is due to inducible proteins which are codified by plasmids and transposons. The other mechanism is observed by a decrease in the affinity between the ribosome and the Tetracycline-Mg^{2+} complex due to mutations on the chromosome.

Bromhexine is a bencilamine with expectorant properties. It is used alone or combined with antimicrobial substances for the treatment of respiratory diseases when the production and viscosity of the tracheobranchial mucus is affected.
Bromhexine increases the volume of the bronchial secretions, modifies the mucopolysascharides produced by the secretory cells, decreases the mucus viscosity and increases the activity of the tracheobranchial ciliary action.

4.3 Pharmacokinetic

Doxycycline
The absorption after oral administration is high. The rate of absorption reaches values higher than 70% of the administered dose in most species when it is administered by oral route.

The food intake could modify the oral bioavailability of doxycycline. In a fasting state the bioavailability is 10-15 % higher than when the animal ingests food.

Doxycycline is widely distributed in the organisms due to its physico-chemical characteristics, because it is highly liposoluble. Doxycycline reaches well-perfused and peripheral tissues. Doxycycline is concentrated in the liver, kidneys, bones and gut. In this last case it is because doxycycline undergoes enterohepatic circulation. Doxycycline reaches higher concentrations in the lungs than in plasma. Therapeutic concentrations in aqueous humor, myocardium, reproductive tissues, brain and mammary gland have been detected. The binding to plasmatic proteins is 90-92%. 40 % of the drug is metabolized and widely excreted by faeces (intestinal and biliary route). The major part is excreted as inactive microbiologically conjugates.

BOVINE
Oral administration to young animals in milk produces a bioavailability of 70%. Elimination shelf-life ($t_{1/2}$) is 12 h. Concentrations at steady state (Css) were about 2 µg/ml.

These animals have showed an absence of hepatic metabolism since doxycycline can only be detected in plasma and urine.

Bromhexine

After oral administration, bromhexine is absorbed rapidly. It is rapidly metabolised producing an active metabolite, ambroxol. The excretion occurs in the urine, with a variable excreted percentage in the faeces.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

No information is available on potential interactions or incompatibilities of this veterinary medicinal product administered orally by mixing into drinking water or liquid feed containing biocidal products, feed additives or other substances used in drinking water.

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

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 4 years
Shelf life after first opening the immediate packaging: 6 months
Shelf life after dissolution in milk replacer according to directions: 6 hours

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

5.4 Nature and composition of immediate packaging

Thermosealed bag made of polyester, aluminium and polyethylene complex.

Packaging sizes:

Bag of 200 g
Bag of 1 Kg

Not all pack sizes may be marketed.

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

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

Medicines should not be disposed of via wastewater or household waste.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

LABORATORIOS KARIZOO, S.A.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database.