[Version 9.1,11/2024]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Centidox 1000 mg/g, powder for use in drinking water or milk (replacer) for cattle and pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g contains:

Active substance:
Doxycycline 867 mg
(equivalent to 1000 mg of doxycycline hyclate)

Excipients: None

Yellow powder.

3. CLINICAL INFORMATION

3.1 Target species

Cattle (calf) and pig.

3.2 Indications for use for each target species

Treatment and metaphylaxis of respiratory diseases caused by *Pasteurella multocida* and *Mycoplasma* spp. susceptible to doxycycline. The presence of the clinical disease in the herd should be established before the veterinary medicinal product is used.

3.3 Contraindications

Do not use in animals with an active microbiological digestion in the rumen.
Do not use in cases of hypersensitivity to doxycycline or other tetracyclines.
Do not use in animals with hepatic disorders.
Do not use in animals with renal disorders.

3.4 Special warnings

The uptake of medication by animals can be altered as a consequence of illness. In case of insufficient uptake of drinking water/milk, animals should be treated parenterally.

3.5 Special precautions for use

Special precautions for safe use in the target species:
Administer the medicated milk per calf individually. It should be taken into account that de-mixing may occur in the milk (replacer). To prevent this happening, the mixer should be kept turned on during tapping of the milk.
Due to likely variability (time, geographical) in susceptibility of bacteria for doxycycline, bacteriological sampling and susceptibility testing are recommended. If this is not possible, therapy should be based on local (regional and farm level) epidemiological information about susceptibility of the target bacteria as well as by taking into account official national antimicrobial policies.
Inappropriate use of the veterinary medicinal product may increase the prevalence of bacteria resistant to doxycycline and may decrease the effectiveness of treatment with other tetracyclines due to the potential for cross-resistance.
Avoid administration in oxidised drinking equipment.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to doxycycline or other tetracyclines should avoid contact with the veterinary medicinal product.
During preparation and administration of the medicated drinking water, skin contact with the veterinary medicinal product and inhalation of dust particles should be avoided. Wear impermeable gloves (e.g. rubber or latex) and an appropriate dust mask (e.g. disposable half-mask respirator conforming to European Standard EN149) when applying the veterinary medicinal product.
In the event of eye or skin contact, rinse the affected area with large amounts of clean water and if irritation occurs, seek medical attention. Wash hands and contaminated skin immediately after handling the veterinary medicinal product.
If you develop symptoms following exposure such as skin rash, you should seek medical advice and show this warning to the physician. Swelling of the face, lips or eyes, or difficulty with breathing are more serious symptoms and require urgent medical attention.
Do not smoke, eat or drink while handling the veterinary medicinal product.
Take measures to avoid producing dust when incorporating the veterinary medicinal product into water. Avoid direct contact with skin and eyes when handling the veterinary medicinal product to prevent sensitisation and contact dermatitis.

Special precautions for the protection of the environment:
Not applicable.

3.6 Adverse events

Cattle (calf) and pig:

Rare (1 to 10 animals / 10,000 animals treated):	Allergic reaction Photosensitivity
Undetermined frequency (cannot be estimated from the available data)	Cardiomyopathy[a]

[a] In calf: Acute, sometimes fatal, heart muscle degeneration can occur after one or more administrations. Since in most cases this is related to overdosing, it is important to measure the dose accurately.

If suspected adverse reactions occur, treatment should be discontinued.

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 or immediate packaging for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:
Laboratory studies have not produced any evidence of a teratogenic, foetotoxic or maternotoxic effect. In the absence of specific studies, the use of the veterinary medicinal product is not recommended during pregnancy or lactation.

3.8 Interaction with other medicinal products and other forms of interaction

Do not combine with antibiotics that are bactericidal like penicillins or cephalosporins.
Absorption of doxycycline can be decreased in the presence of high quantities of calcium, iron, magnesium or aluminium in the diet. Do not administer together with antacids, kaolin or iron preparations.

It is advised that the interval between the administration of other veterinary medicinal products containing polyvalent cations should be 1-2 hours, because they limit the absorption of tetracyclines. Doxycycline increases the action of anticoagulants.

3.9 Administration routes and dosage

Calves: In milk (replacer) use.
Pigs: In drinking water use.

Dosage:
Calves: 10 mg doxycycline hyclate per kg body weight per day for 5 days
Pigs: 10 mg doxycycline hyclate per kg body weight per day for 5 days
Calves:
Based on the dose to be used, and the number and weight of the calves to be treated, the exact daily amount of veterinary medicinal product required can be calculated. To ensure a correct dosage, body weight should be determined as accurately as possible to avoid under-dosing. The use of suitably calibrated weighing equipment is recommended if part packs are used.
The following formula can be used to calculate the concentration of the veterinary medicinal product per litre milk (replacer):

$$\frac{\text{10 mg veterinary medicinal product per kg body weight per day} \times \text{average body weight (kg) of animals to be treated}}{\text{average daily milk (replacer) consumption l//animal}} = \text{.... mg veterinary medicinal product per litre of milk (replacer)}$$

After reconstitution with (artificial) milk the solution should be consumed within 6 hours.
The medicated milk (replacer) should not contain less than 100 mg veterinary medicinal product per litre.

Pigs:
A concentrated drinking water solution should be given twice daily (morning/evening) such that half of the total daily dose is consumed per medication period of 4 hours. This drinking water solution should contain at a minimum 400 mg veterinary medicinal product per litre drinking water. Based on the dose to be used, the minimum concentration of 400 mg veterinary medicinal product per litre, mean drinking water consumption, and the number and weight of the pigs to be treated, the exact amount of medicated drinking water required can be calculated. To ensure a correct dosage, body weight should be determined as accurately as possible. The use of suitably calibrated weighing equipment is recommended if part packs are used. For example, a solution containing 400 mg veterinary medicinal product per litre drinking water is sufficient, when given one litre twice per day, to administer the full treatment dose of 10 mg/kg for pigs of 80 kg body weight consuming 100 ml drinking water per kg body weight.
Medicated drinking water solution should be consumed within 4 hours. Do not prepare more medicated drinking water than will be consumed within that 4 hour period. It is advisable to restrict drinking water for approximately 2 hours (less in hot weather) prior to the medication period and to ensure there are enough drinking points for adequate water consumption for all pigs to be treated. No other source of drinking water should be available during the medication period. Once all the medicated water has been drunk, turn the drinking water system back on.
Solubility of the veterinary medicinal product is pH dependent and in areas with hard alkaline water, formation of complexes may occur in the drinking water. The veterinary medicinal product should not be used in very hard water above 17.5°d and pH more than 8.1.

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

Overdosing in calves could in some cases result in an acute, sometimes fatal heart muscle degeneration, see also 3.6.

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

3.12 Withdrawal periods

Calves:
Meat and offal: 16 days
Pigs:
Meat and offal: 8 days

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code : QJ01AA02

4.2 Pharmacodynamics

Doxycycline is a broad spectrum antibiotic. It inhibits the bacterial protein synthesis intracellularly by binding to the 30S ribosome subunits. The access of amino acetyl-tRNA to the acceptor place of the mRNA-ribosome complex is blocked in this manner, which prevents the fixation of amino acids to the forming peptide chains.
Tetracyclines are bacteriostatic antibiotics with activity against a wide range of aerobic and anaerobic gram-positive and gram-negative bacteria. They are also effective against Mycoplasmata.
Four resistance mechanisms acquired by micro-organisms against tetracyclines in general have been reported: decreased accumulation of tetracyclines (decreased permeability of the bacterial cell wall and active efflux), protein protection of the bacterial ribosome, enzymatic inactivation of the antibiotic and rRNA mutations (preventing the tetracycline binding to ribosome). Tetracycline resistance is usually acquired by means of plasmids or other mobile elements (e.g. conjugative transposons). Cross-resistance between tetracyclines has also been described. Due to the greater liposolubility and greater facility to pass through cell membranes (in comparison to tetracycline), doxycycline retains a certain degree of efficacy against micro-organisms with acquired resistance to tetracyclines.

4.3 Pharmacokinetics

Doxycycline is rapidly and almost completely absorbed from the intestinal tract. Feeding can modify the oral bioavailability of doxycycline. Distribution of doxycycline in the body and penetration in most tissues is good.
Following absorption tetracyclines are hardly metabolised. Doxycycline is - contrary to other tetracyclines - primarily excreted with the faeces.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.
The solubility of the veterinary medicinal product is pH dependent and it will precipitate if mixed in an alkaline solution.
Do not store the drinking water in metallic containers.
No information is available on potential interactions or incompatibilities of this veterinary medicinal product administered orally by mixing into drinking water containing biocidal products or other substances used in drinking water.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 6 months.
Shelf life after dissolution according to directions:
Solutions in water: 4 hours.
Milk solutions: 6 hours.

5.3 Special precautions for storage

Keep the bag tightly closed after first opening in order to protect from moisture.

5.4 Nature and composition of immediate packaging

Pack sizes of 100 g, 250 g, 500 g, 1 kg and 10 x 100 g alufoil sachets in a carton box.
The packs consists of one of the following laminates:
- Sachet with outside a white layer, inside different transparent layers, a sub-layer of aluminium and an inner layer of polyethylene.
- Sachet with an outer layer of polyester, middle layers of polyethylene and aluminium and an inner layer of an ionomer (Surlyn).
- Sachet with an outer layer of polyethylene terephtalic acid, middle layers of aluminium and polyamide and an inner layer of polyethylene.

Not all pack sizes may be marketed.

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

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

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.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

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 (https://medicines.health.europa.eu/veterinary).