ANNEX III

LABELLING AND PACKAGE LEAFLET

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE
COMBINED LABEL AND PACKAGE LEAFLET

PP Container/bucket

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
Dopharma Research B.V.
Zalmweg 24
4941 VX Raamsdonksveer, NL

Manufacturer responsible for the batch release:
Dopharma B.V.
Zalmweg 24
4941 VX Raamsdonksveer, NL

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Doxylin 100%, powder for use in drinking water/ milk for calves and pigs.
Doxycycline hyclate.

3. STATEMENT OF THE ACTIVE SUBSTANCE AND OTHER INGREDIENTS

Doxycycline hyclate 1000 mg/g
(equivalent to doxycycline 867 mg/g)

4. PHARMACEUTICAL FORM

Powder for use in drinking water/ milk.

Yellow, crystalline powder.

5. PACKAGE SIZE

100 grams, 1 kg, 2 kg, 5 kg

6. INDICATIONS

Pre-ruminating calves:
- Bronchopneumonia and pleuropneumonia caused by *Pasteurella spp*, *Streptococcus spp*, *Arcanobacterium pyogenes*, *Haemophilus somnus* and *Mycoplasma spp*.

Pigs:
- Atrophic rhinitis caused by *Pasteurella multocida* and *Bordetella bronchiseptica*;
- Bronchopneumonia caused by *Pasteurella multocida*, *Streptococcus suis* and *Mycoplasma hyorhinis*;
- Pleuropneumonia caused by *Actinobacillus pleuropneumoniae*.

7. CONTRAINDICATIONS

Do not use in case of hypersensitivity to tetracyclines.
Do not administer to animals with severe liver- or kidney insufficiency.

8. ADVERSE REACTIONS

In calves acute, sometimes fatal myocardial degeneration can occur following single or multiple dosages. Since mostly this is caused by overdosage, it is important to measure the dosage accurately.
Tetracyclines may - in rare cases (more than 1 but less than 10 animals in 10 000 animals treated) - induce photosensitivity and allergic reactions. If suspected adverse reactions occur, treatment should be discontinued.

If you notice any side effects, even those not already listed in this label or you think that the medicine has not worked, please inform your veterinary surgeon.

9. TARGET SPECIES

Cattle (pre-ruminating calves) and pigs.

10. DOSAGE FOR EACH SPECIES, ROUTE AND METHOD OF ADMINISTRATION

Calves	10 mg of doxycycline hyclate/kg of body weight/day, for 3-5 consecutive days, divided over 2 administrations.
Pigs:	10 mg of doxycycline hyclate/kg of body weight/day, for 3-5 consecutive days.

Mode of administration:
Calves: orally, dissolve in the milk(replacer)
Pigs: orally, dissolve in the drinking water

11. ADVICE ON CORRECT ADMINISTRATION

For the administration through the drinking water, the exact daily amount of product should be calculated, based on the recommended dose, and the number and weight of the animals to be treated, according to the following formula:

$$\frac{\text{mg of product / kg of body weight / day} \times \text{mean body weight (kg) of animals to be treated}}{\text{mean daily water consumption (litre) per animal}} = \text{.... mg of product per litre of drinking water}$$

To ensure a correct dosage body weight should be determined as accurately as possible.
The uptake of medicated water is dependent on the clinical conditions of the animals. In order to obtain the correct dosage, the concentration in drinking water may have to be adjusted.
The use of suitably calibrated weighing equipment is recommended if part packs are used. The daily amount is to be added to the drinking water such that all medication will be consumed in 24 hours. Medicated drinking water should be freshly prepared every 12 hours. It is recommended to prepare a concentrated pre-solution – max. 400 grams of product per 10 litres of drinking water - and to dilute this further to therapeutic concentrations if required. Alternatively, the concentrated solution can be used in a proportional water medicator.

Solubility of the product is pH dependent and in areas with hard alkaline water formation of complexes may occur in the drinking water.
The product should not be used in very hard water above 16°d and pH more than 8.
Do not store the drinking water in metallic containers.
The medicated milk replacer should be used within 6 hours.

12. WITHDRAWAL PERIOD

Withdrawal periods:
Calves (meat and offal): 14 days.
Pigs (meat and offal): 8 days.

13. SPECIAL STORAGE PRECAUTIONS

Keep the container tightly closed in order to protect from light and moisture.

Do not use this veterinary medicinal product after the expiry date which is stated on the label after EXP.

14. SPECIAL WARNINGS

Special warnings for each target species

The uptake of medication by animals can be altered as a consequence of illness. In case of insufficient uptake of drinking water or medicated milk replacer, animals should be treated parenterally.
It is necessary that the medicated milk is administered to each calf individually. Also the separation of doxycycline in the milk replacer has to be taken into account. In order to prevent this, leave the mixer on during the tapping of the milk.

Special precautions for use in animals
Due to likely variability (time, geographical) in susceptibility of bacteria for doxycycline, bacteriological sampling and susceptibility testing of micro-organisms from diseased animals on farm are highly 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 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
Resistance to tetracyclines has been reported in pig respiratory pathogens (*A. pleuropneumoniae, S. suis*,) and calf pathogens (*Pasteurella spp*) in some EU countries.

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.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
If you know you are allergic to the tetracycline class of antibiotics, special care should be taken when handling this product or the medicated solution.
To prevent sensitization and contact dermatitis during preparation and administration of the medicated drinking water, skin and eye contact with the 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 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 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 product.

Pregnancy and lactation
Due to deposit of doxycycline in young bone tissue, use of the product should be limited during pregnancy and lactation.

Interactions with other medicinal products and other forms of interaction
Do not use in conjunction with bactericidal antibiotics, such as penicillins and cephalosporins.
Absorption of doxycycline can be decreased in the presence of high quantities of calcium, iron, magnesium or aluminium in the diet. Do not administered together with antacids, kaolin and iron preparations.
It is advised that the interval between the administration of other products containing polyvalent cations should be 1-2 hours because they limit the absorption of tetracyclines.
Doxycycline increases the action of anticoagulants.

Overdose (symptoms, emergency procedures, antidotes)
In calves an acute, sometimes fatal myocardial degeneration can occur following overdose. (See also the section Adverse reactions). Symptomatic treatment should be initiated if necessary.

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

15. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

16. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

17. OTHER INFORMATION

List of pack sizes:
- Container: 100 grams, 1 kg
- Bucket: 1, 2, 5 kg

Not all pack sizes may be marketed.

18. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only - to be supplied only on veterinary prescription

19. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

20. EXPIRY DATE

EXP << >>

Shelf life after first opening the container: 3 months
Shelf-life after reconstruction in drinking water: 12 hours
Shelf-life after reconstruction in milk replacer: 6 hours

Once opened, use by __/__

21. MARKETING AUTHORISATION NUMBER

22. MANUFACTURER'S BATCH NUMBER

Batch << >>