ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Doxylin 100%, powder for use in drinking water/milk for calves and pigs (NL, BE, DE, EE, EL, LT, LV)
Doxylin 1000 mg/g, powder for use in drinking water/milk for calves and pigs (IT, HU, RO)
Doxylin, 867 mg/g, powder for use in the drinking water/milk for calves and pigs (FR)
Doxymed (DK), 1000 mg/g, powder for use in the drinking water/milk for calves and pigs (PL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

Active substance:

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

3. PHARMACEUTICAL FORM

Powder for use in drinking water/milk.
Yellow, crystalline powder.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (pre-ruminating calf), pigs

4.2 Indications for use, specifying the target species

Pre-ruminating calves:
- Bronchopneumonia and pleuropneumonia caused by *Pasteurella spp*, *Streptococcus spp*, *Trueperella pyogenes*, *Histophilus somni* 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*.

4.3 Contraindications

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

4.4 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 to administer medicated milk to calves on an individual basis. 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.

4.5 Special precautions for use

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.

4.6 Adverse reactions (frequency and seriousness)

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.

4.7 Use during pregnancy, lactation or lay

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

4.8 Interaction 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 administer 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.

4.9 Amounts to be administered and administration route

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

Dosage:

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.

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:

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

To ensure a correct dosage body weight should be determined as accurately as possible.
The uptake of medicated water is dependant 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.

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

In calves an acute, sometimes fatal myocardial degeneration can occur following overdose (see also 4.6). Symptomatic treatment should be initiated if necessary.

4.11 Withdrawal period

Meat and offal:
Calves: 14 days.
Pigs: 8 days.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterial for systemic use, tetracyclines

ATCvet-code: QJ01AA02

5.1 Pharmacodynamic properties

Doxycycline is a broad-spectrum antibiotic. It inhibits bacterial protein synthesis intracellularly by binding on the 30-S ribosome subunits. This interferes with binding of aminoacetyl-tRNA to the acceptor site on the mRNA ribosome complex and prevents coupling of amino acids to the elongating peptide chains.
Doxycycline inhibits bacteria, Mycoplasmata, Chlamydia, Rickettsia, and certain Protozoa.

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 transposones). 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.

MIC values for tetracycline:

Pathogen	**MIC_{50}**	**MIC_{90}**
Mannheimia haemolitica (Bo)	0.5	8
Pasteurella multocida (Bo)	0.5	2
Pasteurella multocida (Su)	0.5	2
Actinobacillus pleuropneumoniae (Su)	1	16
Streptococcus suis (Su)	16	32

5.2 Pharmacokinetic properties

Doxycycline is quickly and almost completely absorbed from the intestine. The presence of food in the intestine has no effect on the actual absorption of doxycycline. The distribution of doxycycline in the body and penetration of doxycycline throughout most body tissues is good. Following absorption, tetracyclines are hardly metabolised. In contrast to the other tetracyclines, doxycycline is mainly excreted via the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Major incompatibilities

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

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening of the immediate packaging: 3 months.
Shelf life after reconstitution in drinking water: 12 hours.
Shelf life after reconstitution in milk replacer: 6 hours.

6.4. Special precautions for storage

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

6.5 Nature and composition of immediate packaging

White polypropylene container of 100 grams or 1 kg, covered with a low-density polyethylene closure.
White polypropylene container (bucket) of 1, 2 or 5 kg, covered with a polypropylene closure.
Not all pack sizes may be marketed.

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

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

7. MARKETING AUTHORISATION HOLDER

Dopharma Research B.V.
Zalmweg 24
4941 VX Raamsdonksveer the Netherlands
research@dopharma.com

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: *To be completed nationally.*

Date of last renewal:

10. DATE OF REVISION OF THE TEXT

To be completed nationally.

PROHIBITION OF SALE, SUPPLY AND/OR USE

Prescription only medicine.