SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Doxyprex 100 mg/g Premix for medicated feeding stuff for pigs (after weaning)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

Active substance:
100 mg of Doxycycline base as hyclate
Excipients:
Semoline q.s.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff
Yellow granules.

4. CLINICAL PARTICULARS

4.1. Target species

Pigs (after weaning)

4.2. Indications for use, specifying the target species

For the treatment and prevention of porcine respiratory disease caused by *Pasteurella multocida* and *Bordetella bronchiseptica,* susceptible to doxycycline, when the disease has been diagnosed in the herd.

4.3. Contraindications

Do not use in cases of hypersensitivity to tetracyclines.
Do not use in animals with hepatic damage.

4.4. Special warnings for each target species

The uptake of medicated feed by animals can be altered as a consequence of illness. In case of insufficient feed intake, animals should be treated parenterally.

4.5. Special precautions for use

Special precautions for use in animals

Due to variability in susceptibility of bacteria for doxycycline, use of the product should be based on bacteriological sampling and sensitivity testing or recent experience on the farm and take into account official and local antimicrobial policies.

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

Avoid handling the product if hypersensitivity to tetracyclines exists.

Care should be taken to avoid contact with the product during its incorporation to the feed as well as during the administration of the medicated feed to the animals.

Adequate measures should be taken to avoid powder dissemination during the incorporation of the product to the feed.

It is recommended to use a non-powder mask (according to the EN140FFP1 regulation), gloves, working suit and approved safety glasses.

Avoid skin and eye contact. In case of accidental contact with eyes and spillage onto skin, wash the exposed area with plenty of clean water.
Do not smoke, eat or drink while handling the product.
If symptoms appear after exposition as a skin eruption, seek medical advice and show the package leaflet to the physician. Inflammation of the face, lips and eyes or respiratory difficulty are more severe signs that require urgent medical attention.

4.6. Adverse reactions (frequency and seriousness)

Allergic reactions and photosensitivity may appear, as for all tetracyclines.
Digestive alterations by intestinal dysbiosis may appear in very long-term treatments.

4.7. Use during pregnancy, lactation or lay

The use is not recommended during pregnancy and lactation.

4.8. Interaction with other medicinal products and other forms of interaction

Absorption of doxycycline may be diminished in the presence of high quantities of Ca, Fe, Mg or Al in the diet. Do not administer together with antacids, kaolin and iron preparations.
Do not administer in conjunction with bactericidal antibiotics like beta-lactames.

4.9. Amounts to be administered and administration route

In feed use.

The recommended dose is 10 mg of doxycycline/kg of body weight/day (equivalent to 1 g of Doxyprex/10 kg of b.w.) for 7 consecutive days. For pigs with a daily consumption of 40 g of feed/kg b.w./day this dose corresponds to 250 mg of doxycycline per kg of feed which gives a rate of incorporation of 2.5 kg/Ton. The feed consumption will depend on the clinical condition of the animal. In order to obtain a correct dosage, the concentration of the product should be adjusted taking into account the daily feed intake at the onset of treatment.

The following calculation can be used to calculate dosage:
1 mg Doxyprex/kg feed = 10 mg doxycycline/kg b.w. x 10 x bodyweight (kg)/Daily feed intake (kg)

Mixing instructions:
The premix is only intended to be incorporated into granulated medicated feeding stuffs.
A horizontal ribbon mixer should be used to incorporate the product into the feeding stuff. It is recommended that one part of Doxyprex is first mixed into one part of the feeding stuff, followed by the rest of the feeding stuff and mixed well. Medicated feed may then be

granulated. Pelleting conditions involve preconditioning ingredients with steam at 55-65ºC and 10% moisture. Before granulation, flour should not reach a temperature higher than 55 ºC.

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

No symptoms of intolerance to the product have been detected in the studies conducted in which a medicated feed with 600 ppm (2.4 times the recommended dose) was administered to the 20-30 kg animals during twice the recommended period.

4.11. Withdrawal period

Meat and offal: 7 days.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use. Tetracyclines, ATCvet code: QJ01AA02.

5.1. Pharmacodynamic properties

Doxycycline is a broad spectrum antibiotic with bacteriostatic activity that acts by interfering on the bacterial protein synthesis of the sensitive species.

Doxycycline is a semi-synthetic tetracycline derived from oxytetracycline that acts on the 30S ribosomal bacterial subunit in a reversible union, by blocking the binding of aminoacyl-tRNA (transference RNA) to the mRNA/ribosome complex, avoiding the addition of new amino acids to the growing peptide chain and interfering therefore on the protein synthesis.

It is active against:
Pasteurella multocida and *Bordetella bronchiseptica*

"In Spain during 2001, the *in vitro* sensitivity to doxycycline has been determined against porcine strains of *Pasteurella multocida* and *Bordetella bronchiseptica* resulting in MIC_{90} values of 0.795µg/ml and 0.053µg/ml respectively."

According to the Clinical and Laboratory Standard (CLSI) regulation, organisms other than streptococci with MIC values ≤ 4 µg/ml are considered sensitive, at 8 µg/ml intermediate and with MIC values ≥ 16 resistant to doxycycline.

At least two mechanisms of resistance to tetracyclines exist. The most important mechanism is due to the decrease of the cellular accumulation of the drug. It is due to the establishment of an elimination route by pumping the antibacterial agent or to an alteration in the transport system, resulting in a limited tetracycline energy-dependent capture to the exterior of the cell. Alteration in the transport system is produced by inducible proteins codified in plasmids and transposons. The other mechanism is evidenced by a reduction in the affinity of the ribosome for the Tetracycline-Mg^{2+} complex due to mutations in the chromosome. Cross-resistance is frequent between tetracyclines.

5.2. Pharmacokinetic particulars

Absorption after oral and intramuscular administration is high. After oral administration, in most species values higher than 70% of administered doses are reached.

Food can slightly modify oral bioavailability of doxycycline.

Doxycycline is widely distributed throughout the organism due to its physico-chemical characteristics, provided that is highly lipid-soluble. It reaches well irrigated and peripheral tissues. It is concentrated in liver, kidney, bones and intestine; in this last case it is due to an enterohepatic cycle. Concentrations that reaches in lung are always higher than in plasma. Therapeutic concentrations have been detected in watery humor, myocardium, reproductive tissues, brain and mammary gland. Binding to plasmatic proteins is about 90-92%. A 40% of the drug is metabolised and largely excreted in faeces (bile and intestinal route), mostly as conjugates microbiologically inactive.

Pigs (after weaning)
Oral bioavailability of doxycycline ranges between 50-60% values. Once absorbed, the drug is bound in a very high percentage (93%) to plasmatic proteins.
Provided its lipophilic properties doxycycline is easily distributed in animal tissues, showing volumes of distribution of 0.53 l/kg. Its hepatic metabolism is scarce, showing traces of some metabolites at kidney level. Its excretion is carried out through the intestinal mucous and in a lower extent, through bile excretion, resulting in plasmatic clearance values of 1.7 ml/min/kg.

Following single dose administration, C_{max} was 1.70 μg/ml with a T_{max} of 6 hours. Administration of the product according to the recommended posology results in a maximum plasmatic concentration at steady of 2.0 -0.4 μg/ml. After withdrawal of medication, half-life of the terminal phase is of 6 h. It is mainly eliminated through the small intestine that supposes an advantage in relation to the rest of tetracyclines provided that it is not accumulated in the organism when renal function is diminished since it is not its mainly route of elimination.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Liquid sorbitol, non-crystallising
Liquid paraffin
Semoline *(declared on labelling as carrier)*

6.2. Major Incompatibilities

Do not administer with oxidant substances.
Do not mix with any other veterinary medicinal product.

6.3. Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf-life after first opening the immediate packaging: 3 months.
Shelf-life after incorporation into meal or pelleted feed: 3 months.

6.4. Special precautions for storage

Store below 30 ºC.
After first opening, keep the pack tightly closed. Store in a dry place.

6.5. Nature and composition of immediate packaging

Containers of 1 kg, 5 kg, 20 kg and 25 kg.

Thermosealed bags of a complex film made of polyester external layer, aluminium intermediate layer and polyethylene internal layer that is in contact with the product.

In the 5 kg, 20 kg and 25 kg presentations, bags contain an additional intermediate nylon layer. The closure is by thermosealing.
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 materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

04/02/2004

10. DATE OF REVISION OF THE TEXT

{<DD/MM/YYYY>}

PROHIBITION OF SALE, SUPPLY AND/OR USE
Not applicable.