SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ladoxyn 100 mg/g premix for medicated feeding stuff for pigs
(in Austria, Cyprus, Hungary, Italy, Portugal and Slovakia)
Ladoxyn 100 mg/g premix pro medikaci krmiva
(in Czech Republic)
Ladoxyn 100 mg/g Premezcla
(in Spain)
Pulmodox 100 mg/g premix for medicated feeding stuff for pigs
(in Germany, Greece and United Kingdom)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One g premix for medicated feeding stuff contains:

Active substance:	Doxycycline (as hyclate)	100.0 mg
	(equivalent to 115.4 mg doxycycline hyclate)	

Excipients: lactose monohydrate
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff.
Yellow, free-flowing granules.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs (weaned piglet).

4.2 Indications for use, specifying the target species

Treatment and prevention of clinical respiratory infections caused by *Mycoplasma hyopneumoniae* and *Pasteurella multocida* susceptible to doxycycline. The presence of disease in the herd should be established before use.

4.3 Contraindications

Do not use in case of hypersensitivity to the active substance or to any of the excipients.
Do not use when tetracycline resistance has been detected in the herd due to the potential of cross resistance.

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 feed, animals should be treated parenterally.

4.5 Special precautions for use

Special precautions for use in animals

Inappropriate use of the veterinary medicinal product may increase the prevalence of bacteria resistant to tetracycline due to the potential for cross resistance.
Use of the veterinary medicinal product should be based on susceptibility testing and take into account official and local antimicrobial policies.
The use of the veterinary medicinal product should be limited to herds where the disease has been diagnosed.

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

Handle this veterinary medicinal product with care to avoid exposure during incorporation into feed and administration of medicated feed to the animals, taking all recommended precautions. Mix the veterinary medicinal product into feed evenly and hygienically. Take adequate measures to avoid dust formation when incorporating the veterinary medicinal product into feed. Wear dust mask, gloves, overalls and approved safety glasses. Direct contact of the veterinary medicinal product with the skin, eyes and mucous membranes should be avoided. In case of accidental exposure rinse abundantly with water. Do not smoke, eat or drink when handling the veterinary medicinal product.
People with known hypersensitivity to tetracyclines should avoid contact with the veterinary medicinal product.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Inflammation of the face, lips or eyes or respiratory difficulties are the most serious signs which require urgent medical attention.

4.6 Adverse reactions (frequency and seriousness)

As for all tetracyclines, on very rare occasions allergic reactions and photosensitivity may occur. If suspected adverse reactions occur, treatment should be discontinued. Inform your veterinary surgeon if adverse reactions occur that are not indicated.

4.7 Use during pregnancy, lactation

Laboratory studies in rats and rabbits have not produced any evidence of a teratogenic, foetotoxic, maternotoxic effects.

The safety of “Ladoxyn 100 mg/g premix for medicated feeding stuff for pigs” has not been established in pregnant or lactating sows. The use is not recommended during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interaction

Do not incorporate the veterinary medicinal product in feed overloaded with polyvalent cations such as Ca^{2+}, Mg^{2+}, Zn^{2+} and Fe^{3+} because the formation of doxycycline complexes with these cations is possible. Do not administer together with antacids, kaolin and iron preparations and in conjunction with bactericidal antibiotics like beta-lactames.
Doxycycline increases the action of anticoagulants.

4.9 Amounts to be administered and administration route

To be administered orally, in medicated feeding stuff.

Dosage:

12.5 mg doxycycline per kg of body weight daily, administered for 8 days.

Administration:

An inclusion rate of 2.5 g Ladoxyn 100 mg/g premix for medicated feeding stuff for pigs (equivalent to 250 mg doxycycline) per kg of feed should provide the recommended dose in growing pigs between 10 and 50 kg of body weight. When medicating larger pigs including breeding animals or where inappetance occurs, the inclusion level may need adjusting as follows to give the correct dose.

Example: Dose - 12.5 mg doxycycline per kg of body weight.

$$\frac{\text{.....mg Ladoxyn 100 mg/g premix per kg body weight and day} \times \text{Average pig body weight (kg)}}{\text{Average daily feed intake (kg/animal)}} = \text{....mg Ladoxyn 100 mg/g premix per kg of feed}$$

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing. The required doses should be measured by suitably calibrated weighing equipment. To achieve good mixture and homogeneity of incorporation, the use of a pre-mixture is recommended. The required quantity of veterinary medicinal product is thoroughly mixed with a feed ingredient of similar physical nature in the proportion: 1 part Ladoxyn 100 mg/g premix to 10 parts feed ingredient. This pre-mixture is added to the mixer containing the feeding stuff ingredients and mixed thoroughly to produce a homogeneous medicated feeding stuff for incorporation into dry food at the registered mill. Medicated feed may be pelleted using a pre-conditioning step with steam at temperatures not exceeding 75°C.

A manufacturer who is approved to incorporate directly at any concentration, veterinary medicinal products or premixtures containing such products must be responsible for mixing when incorporation is less than 2 kg per tonne for final feed.

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

During the target animal tolerance study, no adverse effect was observed even at the threefold therapeutic dose administered for two times the recommended duration.
If suspected toxic reactions do occur due to extreme overdose, the medication should be discontinued and appropriate symptomatic treatment should be initiated if necessary.

4.11 Withdrawal period(s)

Meat and offal: 7 days.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: tetracyclines, ATCvet code: QJ01AA02

5.1 Pharmacodynamic properties

Doxycycline is a semisynthetic tetracycline derivative. It acts by inhibiting protein synthesis at the ribosomal level, predominantly by binding to the 30S ribosomal subunits of bacteria. Doxycycline is a broad-spectrum antibiotic. It exhibits a wide range of activity against gram-positive and gram-negative, aerobic and anaerobic pathogens, especially against *Pasteurella multocida* and *Mycoplasma hyopneumoniae* isolated from pig respiratory infections. Due to its higher lipid-solubility, that makes the diffusion through the bacterial membrane easier, doxycycline exerts greater *in vitro* against activity than first generation tetracyclines. The MIC_{90} values of doxycycline against *Mycoplasma hyopneumoniae* strains isolated in Spain (2001) and in Belgium (2000-2002) were determined as 0.2 and 0.5 µg/ml, respectively. The MIC_{90} values for *Pasteurella multocida* isolated in France and the United Kingdom (2002-2004), and Germany (2004-2006) were found to be 2.0 µg/mL.
The resistance rate of *M. hyopneumoniae* and *P. multocida* isolates against doxycycline is low (0-6%). Resistance is mostly due to interference with the active transport of the tetracyclines into, and increased efflux from the cells, or ribosomal protection in which protein synthesis becomes resistant to inhibition. Basically there is a complete cross-resistance within the class of tetracyclines. Doxycycline may be effective against certain strains resistant to conventional tetracyclines due to ribosomal protection or efflux pump mechanisms.
According to the CLSI regulation, organisms other than streptococci with MIC values ≤ 4µg/ml are considered sensitive, at 8 µg/ml intermediate and with MIC values ≥ 16µg/m resistant to doxycycline.

5.2 Pharmacokinetic particulars

After oral administration to pigs, doxycycline is substantially absorbed from the gastrointestinal tract, reaching peak serum concentrations between 1.5 and 3 hours after dosing. The bioavailability of doxycycline after oral administration in medicated feed to pigs was found to range between 40 and 50%. The binding rate to plasma proteins is 93%. It is widely distributed in the organisms; at the steady state, the volume of distribution (V_{SS}) is 1.2 L/kg. Doxycycline is not metabolised to any significant extent and it is excreted primarily in faeces, mostly in a microbiologically inactive form. The elimination half-life was reported to be 4-4.2 hours in pigs. The steady-state plasma concentrations of doxycycline after repeated oral administrations of Ladoxyn 100 mg/g premix for medicated feeding stuff for pigs at a dose of 250 mg/kg feed ranged from 1.29 to 2.00 µg/ml, with a mean of 1.61±0.50 µg/ml. Both the lung and nasal mucosa concentrations at steady-state were higher than the plasma level. The ratio between tissue- and plasma concentration was found to be 1.2 for lung and 2.5 for nasal mucosa. The doxycycline concentrations both in the lung and the nasal mucosa exceeded the MIC_{90} of the drug against the target respiratory pathogens.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Povidone
Lactose monohydrate

6.2 Incompatibilities

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

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years
Shelf-life after first opening the immediate packaging: 3 months
Shelf-life after incorporation into meal or pelleted feed: 3 months
The product may be incorporated into pelleted feed, conditioned at a maximum temperature of 75 ºC.

6.4. Special precautions for storage

Do not store above 25°C.
Store in the original container in order to protect from moisture.
Keep the plastic container tightly closed, or re-close the paper bag mechanically as much as possible.

6.5 Nature and composition of immediate packaging

1.25 kg polypropylene container with inner bag of LDPE.
6.25 kg polypropylene container with inner bag of LDPE.
12.5 kg polypropylene container with inner bag of LDPE.
12.5 kg multiwalled, polyethylene layered paper bag.
25 kg multiwalled, polyethylene layered paper bag.
Not all pack sizes may be marketed.

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

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

7. MARKETING AUTHORISATION HOLDER

Lavet Pharmaceuticals Ltd.
H-1161 Budapest
Ottó u. 14.
Hungary

8. MARKETING AUTHORISATION NUMBER

Vm 32823/4000

9. DATE OF FIRST AUTHORISATION

06 November 2008

10. DATE OF REVISION OF THE TEXT

October 2012

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

In Italy:

Ricetta medico veterinaria in triplice copia non ripetibile.