[Version 8.1,01/2017]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Alphadoxan 100 mg/g Premix for Medicated Feeding Stuff for Pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:
Active substance:
100 mg doxycycline (as 115,4 mg doxycycline hyclate)
Excipients:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Premix for Medicated Feeding Stuff
Pale yellow or yellow coloured powder with characteristic odour without mechanical impurities; no knots or clusters.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs

4.2 Indications for use, specifying the target species

For the treatment of clinical signs associated with porcine respiratory disease caused by *Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica* and infections caused by *Streptococcus suis* susceptible to doxycycline in pigs.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in cases of liver or kidney failure.
Do not use in cases of known resistance to tetracycline.

4.4 Special warnings for each target species

Animals showing a poor general condition and/or a decreased appetite should be treated by the parenteral route.

4.5 Special precautions for use

Special precautions for use in animals

This veterinary medicinal product may only be used to treat a stock in which a particular disease in the indication has been diagnosed
The product should be used in conjunction with susceptibility testing and take into account official and local policy relating to the use of antimicrobials.
Use of the product deviating from the instructions may increase the prevalence of bacteria resistant to the doxycycline.
Instead of prolonged and repeated treatment, it has to be changed in stock management, primarily by improving hygiene conditions, proper ventilation, and re-conditioning the stress-free environment.

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

People with known hypersensitivity to tetracyclines should avoid contact with the veterinary medicinal product.
The dust of this product might be mildly irritant to eyes and skin and to airways.
Direct contact of product with skin and eye must be avoided. Avoid the inhalation the dust of product.
Children should always be prevented from getting access to the product.
Product must be handled carefully. During preparation and administration of the medicated feeding stuff, direct contact with the veterinary medicinal product (inhalation, swallowing, eye or skin contacts) should be avoided.
Wear personal protective equipment, like impermeable gloves, protective clothes, and appropriate dust mask when preparing and applying the product.
Wash hands after use. Use the product in well-ventilated area only.
Product must be kept out of reach of children.
The contaminated skin surface and eye must be rinsed with plenty of water. Following accidental inhalation calling medical aid if necessary.
In case of developing allergic symptoms following exposure such as skin rash, perspiration or difficulty with breathing require urgent medical attention and show this warning to the physician.

4.6 Adverse reactions (frequency and seriousness)

Allergic reactions and photosensitivity reactions can occur.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Do not administer doxycycline in feeding stuff containing high quantities of polyvalent cations (as calcium, iron), because doxycycline makes complexes with them. Do not administer doxycycline in combination with bactericidal antibiotics, such as penicillins, cephalosporins and polymixins.

4.9 Amounts to be administered and administration route

Oral use. In feed use.

Dosage:
10 mg doxycycline per kg body weight (bw) per day, administered for 5 consecutive days
The feed intake depends on the clinical condition of the animals, therefore the mixing ratio should be calculated on the basis of the current feed consumption.

Administration:
To ensure the above dose, the exact amount of the medicated feed premix to be fed should be calculated according to the following formula.

… mg doxycycline per kg body weight and day	x	Average pig body weight (kg) of the treated animals	x	Number of the treated animals	=	mg doxycycline per kg of feed
Average daily feed intake (kg)						

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing. The recommended dose and duration of treatment should not be exceeded.
Pelleting of the incorporated feed is allowed at 75 ^{0}C highest temperature.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary
Not known.
4.11 Withdrawal period(s)

Pigs:
Meat and offal: 8 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antimicrobials for systemic use, tetracyclines
ATC vet code: QJ01AA02

5.1 Pharmacodynamic properties

Doxycycline is a bacteriostatic antibiotic that acts by interfering with the bacterial protein synthesis of sensitive species. With diffusion through the outer cell membrane, it passes through the active cytoplasmic membrane via active transport. In the cells it acts on the subunit 30S of the bacterial ribosome, to which is bound irreversibly, blocking the union between aminoacyl-tRNA (transfer RNA) to the mRNA-ribosome complex. This binding effect prevents the addition of new aminoacids into the growing peptide chain and thus interfering with protein synthesis.

There are 4 main mechanisms of acquired resistance to tetracyclines, which include: several efflux pumps; ribosome protection proteins, which bind to the ribosome and remove the tetracyclines from there; monooxygenase enzymes, which enhance the degradation of the antibiotic; and the reduction of the binding affinity between the ribosome and the antibiotic.
Efflux pumps are the most frequently found mechanisms in tetracycline resistant bacteria, however these are less effective against second generation doxycycline and minocycline, compared to the original tetracyclines.

In the CLSI Guideline 2018, Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals, the following breakpoints can be found in connection with the target bacteria:
Actinobacillus pleuropneumoniae, Pasteurella multocida and *Streptococcus suis* susceptibility to tetracycline in swine: Susceptible: $\leq$ 0.5 µg/ml, Intermediate: 1 µg/ml, Resistant: $\geq$ 2 µg/ml.
For *Bordetella bronchiseptica*, breakpoints for tetracyclines in swine are not determined by the CLSI.

Based on data from the past five years, susceptibility of Hungarian *A. pleuropneumoniae* strains to doxycycline is approximately 50%. The international (European) data shows higher susceptibility of the pathogen to tetracyclines. Most European *P. multocida* strains are susceptible to tetracyclines, including doxycycline (65.8%). Nearly 80% of *B. bronchiseptica* strains are susceptible to tetracyclines in Europe. Tetracyclines' MIC50 value in case of all above-mentioned pathogens is 0.5 µg/ml in Europe. Approximately 74% of Hungarian *S. suis* strains are susceptible to doxycycline.

5.2 Pharmacokinetic particulars

Doxycycline is highly absorbable after oral administration. Plasma concentration remains high for 6-8 hours after administration. Doxycycline is well distributed throughout the body. Doxycycline is primarily excreted through faeces, mainly as microbiologically inactive conjugates.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltodextrin
Cellulose, Microcrystalline
Paraffin, Liquid

6.2 Major 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: 3 years.
Shelf life after first opening the immediate packaging: 6 months.
Shelf life after incorporation into meal or pelleted feed: 3 months.

6.4. Special precautions for storage

Store below 25 °C
Do not refrigerate or freeze.

6.5 Nature and composition of immediate packaging

Three layered paper bags with polyethylene inner layer (open, base) with 10 kg’s of capacity

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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ALPHA-VET Veterinary Ltd.,
H-1194 Budapest, Hofherr A. u. 42., Hungary
Telephone number: +36/22-516-419
Fax number (optional): +36/22-516-416
E-mail: alpha-vet@alpha-vet.hu

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:{DD month YYYY}.

10 DATE OF REVISION OF THE TEXT

{DD month YYYY}

PROHIBITION OF SALE, SUPPLY AND/OR USE

Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds.

LABELLING AND PACKAGE LEAFLET

COMBINED LABEL AND PACKAGE LEAFLET:
Alphadoxan 100 mg/g Premix for Medicated Feeding Stuff for Pigs

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

Marketing authorisation holder: ALPHA-VET Veterinary Ltd., H-1194 Budapest, Hofherr A. u. 42., Hungary.
Manufacturer responsible for batch release: ALPHA-VET Veterinary Ltd., Bábolna Pharmaceutical Plant, H-2943 Bábolna, Köves János út. 13., Hungary.

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Alphadoxan 100 mg/g Premix for Medicated Feeding Stuff for Pigs
Doxycycline

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENTS

Each gram contains:
Active substance:
100 mg doxycycline (as 115,4 mg doxycycline hyclate)
Excipients:
Maltodextrin, Cellulose Microcrystalline, Paraffin Liquid

Pale yellow or yellow coloured powder with characteristic odour without mechanical impurities; no knots or clusters.

4. PHARMACEUTICAL FORM

Premix for Medicated Feeding Stuff

5. PACKAGE SIZE

10 kg

6. INDICATION(S)

For the treatment of clinical signs associated with porcine respiratory disease caused by *Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica* and infections caused by *Streptococcus suis* susceptible to doxycycline in pigs.

7. CONTRAINDICATIONS

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in cases of liver or kidney failure.
Do not use in cases of known resistance to tetracycline.

8. ADVERSE REACTIONS

Allergic reactions and photosensitivity reactions can occur.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

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

9. TARGET SPECIES

Pigs

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

Oral use. In feed use.

Dosage:
10 mg doxycycline per kg body weight (bw) per day, administered for 5 consecutive days
The feed intake depends on the clinical condition of the animals, therefore the mixing ratio should be calculated on the basis of the current feed consumption.

Administration:
To ensure the above dose, the exact amount of the medicated feed premix to be fed should be calculated according to the following formula.

$$\frac{\text{… mg doxycycline per kg body weight and day} \times \text{Average pig body weight (kg) of the treated animals} \times \text{Number of the treated animals}}{\text{Average daily feed intake (kg)}} = \text{mg doxycycline per kg of feed}$$

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing. The recommended dose and duration of treatment should not be exceeded.
Pelleting of the incorporated feed is allowed at 75 ^{0}C highest temperature.

11. ADVICE ON CORRECT ADMINISTRATION

Do not use veterinary medicinal product if you notice any visible signs of deterioration.
To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

12. WITHDRAWAL PERIOD(S)

Pigs: Meat and offal: 8 days.

13. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Store below 25°C.
Do not refrigerate or freeze.
Do not use this veterinary medicinal product after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

14. SPECIAL WARNING(S)

Special precautions for use in animals:
This veterinary medicinal product may only be used to treat a stock in which a particular disease in the indication has been diagnosed
The product should be used in conjunction with susceptibility testing and take into account official and local policy relating to the use of antimicrobials.
Use of the product deviating from the instructions may increase the prevalence of bacteria resistant to the doxycycline.
Instead of prolonged and repeated treatment, it has to be changed in stock management, primarily by improving hygiene conditions, proper ventilation, and re-conditioning the stress-free environment.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to tetracyclines should avoid contact with the veterinary medicinal product.
The dust of this product might be mildly irritant to eyes and skin and to airways.
Direct contact of product with skin and eye must be avoided. Avoid the inhalation the dust of product.
Children should always be prevented from getting access to the product.
Product must be handled carefully. During preparation and administration of the medicated feeding stuff, direct contact with the veterinary medicinal product (inhalation, swallowing, eye or skin contacts) should be avoided.
Wear personal protective equipment, like impermeable gloves, protective clothes, and appropriate dust mask when preparing and applying the product.
Wash hands after use. Use the product in well-ventilated area only.
Product must be kept out of reach of children.
The contaminated skin surface and eye must be rinsed with plenty of water. Following accidental inhalation calling medical aid if necessary.
In the event of eye or skin contact, rinse the affected area with large amounts of clean water.
In case of developing allergic symptoms following exposure such as skin rash, perspiration or difficulty with breathing require urgent medical attention and show this warning to the physician.

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:
Do not administer doxycycline in feeding stuff containing high quantities of polyvalent cations (as calcium, iron), because doxycycline makes complexes with them. Do not administer doxycycline in combination with bactericidal antibiotics, such as penicillins, cephalosporins and polymixins.

Overdose (symptoms, emergency procedures, antidotes):
Not known.

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

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

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment. Medicines should not be disposed of via wastewater or household waste.

16. DATE ON WHICH THE LABEL WAS LAST APPROVED

{DD month YYYY}.

17. OTHER INFORMATION

Container: Three layered paper bags with polyethylene inner layer (open, base) with 10 kg's of capacity.
Package size: 10 kg premix for medicated feeding stuff.
Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorization holder.

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 {month/year}
Shelf life after first opening the container: 6 months.
Shelf life after incorporation into pelleted feed: 3 months.

21. MARKETING AUTHORIZATION NUMBER(S)

Marketing authorization number {number}

22. MANUFACTURER'S BATCH NUMBER

Batch {number}