ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Pulmodox 5% Premix for medicated feeding stuff for pigs (AT DE ES IE IT LU NL PT SE)
Suidox vet 5% Premix for medicated feeding stuff for pigs (DK)
Pulmodox doxycycline 50 pig Premix for medicated feeding stuff (FR)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

Active substance:

Doxycycline ..... 50 mg
(as hyclate form)

Excipient:

Qualitative composition of excipients and other constituents
Whole meal wheat

Yellowish white powder, without caking.

3. CLINICAL INFORMATION

3.1 Target species

Pigs (after weaning).

3.2 Indications for use for each target species

Prevention of clinical respiratory disease due to *Pasteurella multocida* and *Mycoplasma hyopneumoniae* sensitive to doxycycline. The presence of disease in the herd should be established before treatment.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in animals with hepatic dysfunction.
See section 3.7.

3.4 Special warnings

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

3.5 Special precautions for use

Special precautions for safe use in the target species:

Inappropriate use of the product may increase the prevalence of bacteria resistant to tetracycline due to the potential for cross resistance. Use of the product should be based on susceptibility testing and take

into account official and local antimicrobial policies.

Do not use when tetracycline resistance has been detected in the herd/flock due to the potential for cross resistance.

Consideration should be given to improvement of management practice on the farm, mainly in hygiene management, ventilation and pig management avoiding stress conditions.

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.

Handle this product with care to avoid exposure during incorporation of premix into feed and administration of medicated feed to the animals, taking all recommended precautions:

- Take adequate measures to avoid dust formation when incorporation of the product into feed is occurring.
- Personal protective equipment consisting of a dust mask (in compliance with EN140FFP1), gloves, overalls, and approved safety glasses should be worn when handling the veterinary medicinal product.
- Avoid contact with skin and eyes. Rinse thoroughly with water in case of exposure.
- Do not smoke, eat, or drink when handling the product.
- If you develop symptoms following exposure such as skin rash, seek medical advice immediately and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

Special precautions for the protection of the environment:

Not applicable.

3.6. Adverse events

Pigs (after weaning):

Undetermined (cannot be estimated from the available data):	Allergic reaction[1,2] Photosensitivity[1]

[1] As for all tetracycline.
[2] In case of occurrence, the discontinuation of the treatment should be recommended.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:

Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, embryotoxic or maternotoxic effects of doxycycline. Safety of the product in pregnant and nursing sows was not demonstrated. Use of the product in pregnant or nursing females is not recommended.

3.8 Interaction with other medicinal products and other forms of interaction

Do not incorporate the medicated premix 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. As tetracyclines are bacteriostatic antimicrobials, do not administer in conjunction with bactericidal antibiotics like beta-lactames. It is advised that the interval between administration of other products containing polyvalent cations should be 1-2 hours because they limit the absorption of tetracycline.

Doxycycline increases the action of anticoagulants.

3.9 Administration routes and dosage

In feed use.
12.5 mg of doxycycline/kg bodyweight/day for 8 consecutive days. (i.e. 250 mg of doxycycline per kg of complete feed - 5 kg premix per ton of animal feed - according to a daily feed intake of 50 g/kg bw/d).
This premix has to be incorporated in a complete feed, the rate of incorporation should not be below 5 kg/ton.
After incorporation into feed and if for use in the form of pellets, the following conditions have been shown to be suitable: Temperature before extrusion at 55 °C (2 min) and temperature after extrusion at 73 °C (2 min).

The intake of medicated feed depends on the clinical condition of the animals. In order to obtain the correct dosage, the concentration of doxycycline has to be adjusted accordingly. To ensure a correct dosage, body weight should be determined as accurately as possible to avoid underdosing.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

An increase of kidney weight was reported in the safety study in pigs at 3 fold the proposed dosage regimen after a treatment duration 2.6 fold the proposed duration. This finding was not confirmed either from clinical pathological nor from histopathological findings.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Meat and offal: 7 days.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01AA02

4.2 Pharmacodynamics

Doxycycline is a bacteriostatic antibiotic belonging to the tetracycline family. Given its more lipid-soluble feature that makes the diffusion through the bacterial membrane easier, doxycycline exerts a

greater *in vitro* activity than first generation tetracyclines. After penetration into bacteria, doxycycline acts by inhibiting protein synthesis.
Doxycycline exerts its antibacterial activity especially against *Pasteurella multocida* and against *Mycoplasma hyopneumoniae* isolated from pig respiratory infections.

4.3 Pharmacokinetics

The bioavailability of doxycycline administered per os is about 33 %. The binding rate to plasma proteins is 93 %. At steady state, the volume of distribution (Vss) of doxycycline is 1.2 l/kg. After oral administration of doxycycline at the recommended dose of 12.5 mg/kg/day for 8 days, average steady state concentration is 1.2 µg/ml in plasma (with a steady state Cmin of 0.9 µg/ml and a steady state Cmax of 1.5 µg/ml). The accumulation factor (between first and last days) is 1.8. The ratio between tissue- and plasma concentration is 1.3 for lung and 2.3 for nasal mucosa.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

The formation of doxycycline complexes with bivalent Ca^{2+} and trivalent Fe^{3+} cations is possible.

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

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life of the premix after incorporation in the feed: 3 months.

5.3 Special precautions for storage

Do not store above 30 °C.

5.4 Nature and composition of immediate packaging

- Small format 1 paper layer/complex paper/LDPE/Alu/1 paper layer/polyethylene low density bag (5 kg).
- Large format 1 paper layer/complex paper/LDPE/Alu/1 paper layer/polyethylene low density bag (25 kg).
- 5 kg white polypropylene bucket containing a 5 kg transparent polyethylene bag.

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

VIRBAC

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

ANNEX III

LABELLING AND PACKAGE LEAFLET

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE - <u>COMBINED LABEL AND PACKAGE LEAFLET</u>

BAG
BUCKET

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Pulmodox 5% Premix for medicated feeding stuff for pigs (AT DE ES IE IT LU NL PT SE)
Suidox vet 5% Premix for medicated feeding stuff for pigs (DK)
Pulmodox doxycycline 50 pig Premix for medicated feeding stuff (FR)

2. COMPOSITION

Each gram contains:
Active substance:
Doxycycline (as hyclate form) ..... 50 mg

Yellowish white powder, without caking.

3. PACKAGE SIZE

5 kg bag
5 kg bucket
25 kg bag

4. TARGET SPECIES

Pigs (after weaning).

5. INDICATIONS FOR USE

Indications for use

Prevention of clinical respiratory disease due to *Pasteurella multocida* and *Mycoplasma hyopneumoniae* sensitive to doxycycline. The presence of disease in the herd should be established before treatment.

6. CONTRAINDICATIONS

Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in animals with hepatic dysfunction.
See section “Pregnancy and lactation”.

7. SPECIAL WARNINGS

Special warnings:

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

Special precautions for safe use in the target species:

Inappropriate use of the product may increase the prevalence of bacteria resistant to tetracycline due to the potential for cross resistance. Use of the product should be based on susceptibility testing and take into account official and local antimicrobial policies.

Do not use when tetracycline resistance has been detected in the herd/flock due to the potential for cross resistance.

Consideration should be given to improvement of management practice on the farm, mainly in hygiene management, ventilation and pig management avoiding stress conditions.

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.

Handle this product with care to avoid exposure during incorporation of premix into feed and administration of medicated feed to the animals, taking all recommended precautions:
- Take adequate measures to avoid dust formation when incorporation of the product into feed is occurring.
- Personal protective equipment consisting of a dust mask (in compliance with EN140FFP1), gloves, overalls, and approved safety glasses should be worn when handling the veterinary medicinal product.
- Avoid contact with skin and eyes. Rinse thoroughly with water in case of exposure.
- Do not smoke, eat, or drink when handling the product.
- If you develop symptoms following exposure such as skin rash, seek medical advice immediately and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

Pregnancy and lactation:

Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, embryotoxic or maternotoxic effects of doxycycline. Safety of the product in pregnant and nursing sows was not demonstrated. Use of the product in pregnant or nursing females is not recommended.

Interactions with other medicinal products and other forms of interaction:

Do not incorporate the medicated premix 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. As tetracyclines are bacteriostatic antimicrobials, do not administer in conjunction with bactericidal antibiotics like beta-lactames. It is advised that the interval between administration of other products containing polyvalent cations should be 1-2 hours because they limit the absorption of tetracycline.

Doxycycline increases the action of anticoagulants.

Overdose:

An increase of kidney weight was reported in the safety study in pigs at 3 fold the proposed dosage regimen after a treatment duration 2.6 fold the proposed duration. This finding was not confirmed either from clinical pathological nor from histopathological findings.

Major incompatibilities:

The formation of doxycycline complexes with bivalent Ca^{2+} and trivalent Fe^{3+} cations is possible.

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

8. ADVERSE EVENTS

Adverse events

Pigs (after weaning):

Undetermined (cannot be estimated from the available data):
Allergic reaction[1,2] Photosensitivity[1]

[1] As for all tetracycline.
[2] In case of occurrence, the discontinuation of the treatment should be recommended.

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed on this label, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder or the local representative of the marketing authorisation holder using the contact details on this label, or via your national reporting system {national system details}.

9. DOSAGE FOR EACH TARGET SPECIES, ROUTES AND METHOD OF ADMINISTRATION

Dosage for each species, routes and method of administration

In feed use.
12.5 mg of doxycycline/kg bodyweight/day for 8 consecutive days. (i.e. 250 mg of doxycycline per kg of complete feed - 5 kg premix per ton of animal feed - according to a daily feed intake of 50 g/kg bw/d).

10. ADVICE ON CORRECT ADMINISTRATION

Advice on correct administration

This premix has to be incorporated in a complete feed, the rate of incorporation should not be below 5 kg/ton.
After incorporation into feed and if for use in the form of pellets, the following conditions have been shown to be suitable: Temperature before extrusion at 55 °C (2 min) and temperature after extrusion at 73 °C (2 min).

The intake of medicated feed depends on the clinical condition of the animals. In order to obtain the correct dosage, the concentration of doxycycline has to be adjusted accordingly. To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

11. WITHDRAWAL PERIODS

Withdrawal periods

Meat and offal: 7 days.

12. SPECIAL STORAGE PRECAUTIONS

Special storage precautions

Keep out of the sight and reach of children.

Do not store above 30 °C.

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

13. SPECIAL PRECAUTIONS FOR DISPOSAL

Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

14. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

15. MARKETING AUTHORISATION NUMBERS AND PACK SIZES

Pack sizes

5 kg bag

5 kg bucket
25 kg bag

Not all pack sizes may be marketed.

16. DATE ON WHICH THE LABEL WAS LAST REVISED

Date on which the label was last revised

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

17. CONTACT DETAILS

Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:

VIRBAC
1ère Avenue 2065m LID
06516 Carros
France

Manufacturer responsible for batch release:

FC France SAS
8–10 rue des Aulnaies
92420 Magny-en-Vexin
France

Local representatives and contact details to report suspected adverse reactions:

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

18. OTHER INFORMATION

19. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

20. EXPIRY DATE

Exp. {mm/yyyy}

Shelf life of the premix after incorporation in the feed: 3 months.

21. BATCH NUMBER

Lot {number}