

**ANNEX I**

**NAME, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCTS, ANIMAL SPECIES, ROUTES OF ADMINISTRATION, AND MARKETING AUTHORISATION HOLDER**

<b>Member State</b>	<b>Applicant or Marketing Authorisation Holder</b>	<b>Product invented name</b>	<b>Pharmaceutical form</b>	<b>Strength</b>	<b>Animal species</b>	<b>Frequency and route of administration</b>	<b>Recommended dose</b>
Belgium, Czech Republic, Germany, Greece, Spain, France, Italy, The Netherlands, Poland, Portugal and Slovakia	Industrial Veterinaria, S.A. Esmeralda, 19 4° 08950 Esplugues de Ll obregat (Barcelona, Spain)	<b>DOXYPREX</b>	Premix	100 mg/g	Pigs (after weaning)	In feed use	10 mg/kg .bw

**ANNEX II**  
**SCIENTIFIC CONCLUSIONS**

## SCIENTIFIC CONCLUSIONS

### 1. Introduction and background

Doxyprex 100 mg premix presented in 5 kg, 20 kg and 25 kg thermosealed bags containing 100 mg/g doxycycline base as hyclate. In Spain the product has been authorised for the indication the treatment of swine respiratory disease caused by *Pasteurella multocida*, *Bordetella bronchiseptica* and *Mycoplasma hyopneumoniae*.

This is also the indication applied for at the start of the mutual recognition procedure (MRP). Following discussions in the CMD(v), the proposed indication was changed during the course of the MRP to: "For treatment of swine respiratory disease caused by susceptible *Pasteurella multocida*, *Bordetella bronchiseptica* and *Mycoplasma hyopneumoniae* to doxycycline."

Germany notified the EMEA on 30 May 2006 that the CMD(v) failed to reach an agreement regarding the product. Pursuant to Article 33(4) of Directive 2001/82/EC, as amended, the matter was referred to the CVMP.

The reason for this was that the national competent authority of Germany considered that this veterinary medicinal product could present a potential serious risk to animal health on the grounds that the efficacy has not been sufficiently substantiated in the dossier.

The CVMP during its meeting of 21-22 June 2006 started a referral procedure under Article 33(4) of Directive 2001/82/EC, as amended, for Doxyprex 100 mg premix. The Marketing Authorisation Holder (MAH) was requested to substantiate the indication and posology as discussed during the recent MRP. The responses were submitted to the EMEA on 19 December 2006.

### 2. Discussion

In the introduction to the responses the applicant has given a justification for submission of this application on a "well-established use" basis. Within the EU doxycycline-based premix products for pigs at recommended dose rates of 10mg/kg once daily for 5 days are stated as having been authorised since 1985. Similar products with 8 or 10 days treatment durations are also available within the EU.

Annex I of Directive 2001/82/EC as amended by directive 2004/28/EC notes that post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue. Therefore, the CVMP considered that the reports mentioned above give favourable evidence for the safety and efficacy of doxycycline in general, but also for the specific final formulation as marketed in Spain.

#### 1. Pivotal clinical trial with Doxycycline 10% premix

The choice of positive control products and the dosing regiment applied were discussed:

The applicant explained that their choice of positive controls in the pivotal field trial was not intended to compare their product with a product, which had been used for the same proposed posology within the Community for at least 10 years. In fact the two positive controls were selected because at that time there were no doxycycline based premix reference products available in Spain. The positive control products were chosen on the basis that they were also medicated premixes, indicated for use in pigs, which contained a single active substance, which had a spectrum of activity inclusive of those organisms causing the proposed indications. The applicant has explained the choice of dose.

Although the choice of positive controls would not be acceptable when assessed under current standards, the CVMP concluded that the applicant has justified that at the time there were no doxycycline based authorised premix for the proposed indications. The applicant has a justifiable rationale behind the choice of products used as positive controls. In addition, a negative control was used. Given that the statistical analysis is appropriate, this study design can conclude that the actual final formulation has shown field efficacy when compared to a negative control group and has produced at least as good results as a comparator product TM550 (oxytetracycline).

No dose confirmation studies appear to have been presented in the above mentioned study, therefore it is important that the references provided should present robust evidence for the field efficacy of the product.

In the answer to the CVMP question the applicant has not discussed or justified the two doses (200ppm and 300ppm) of Doxyprex applied in the clinical trial. During the MRP the applicant did however explain that the incorporation rates of doxycycline in the feed used in the clinical trial were decided to take into account the variability that would be found in the field in regard to pig body weight and feed consumption. The main object was to try to ensure intake of the proposed dose of 10 mg/kg b.w. It is observed that during the first days of treatment the 300 ppm food incorporation came closest to the recommended dose, but as food consumption picked up this was achieved with 200ppm. The justification was considered acceptable, but the dosing section of the SPC should be amended to better reflect the use as proposed and documented by the applicant. Less emphasis should be put on the standard incorporation of 250 ppm. related to “normal” food consumption. It should also be included that the incorporation rate should be based on average food consumption at time of initiating treatment.

The CVMP/627/01 and GCP guideline stated that the response to therapy must be based on clinical and microbiological criteria wherever possible. The lack of evidence of bacteriological cure should be justified and may affect the wording of the indication.

The applicant has submitted a scientific report on Porcine Respiratory Disease Complex (PRDC) and also pointed out that the above mentioned Guideline were not in effect at time of the study or the initial submission to the Spanish Authority. In the pivotal clinical trial, the presence of *P.multocida* and *B.bronchiseptica* was clearly demonstrated in sick pigs, however no post treatment sampling was done to show bacteriological cure. The applicant justifies that the presence of *M.hyopneumoniae* was not determined by bacteriological methods because it was difficult to isolate at that time. The presence was assumed. The applicant provided evidence of efficacy of the active substance, doxycycline, against *M.hyopneumoniae* in pigs from published literature and from MIC studies. These are all references provided with the original submission.

Farms were selected if at least 20% of pigs were showing clinical signs of respiratory disease. The actual groups of pigs studied were all showing clinical signs. The clinical end points were “Time to clinical cure” and “overall clinical cure”. Relapses were assessed. In the practical situation, the premix is usually fed to pigs showing clinical signs and incontact pigs, therefore this active substance is for controlling the clinical signs of disease. Efficacy against *M. hyopneumoniae* has furthermore not been established in the field study, since its presence was not demonstrated.

The CVMP considers that the fact that no post treatment bacteriological samples were taken mean that bacteriological cure cannot be assumed or claimed.

For these reasons, the appropriate proposed indication is suggested as follows:

“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. “

*The Committee agreed that all prudent use recommendations should be put under 4.5. Due to variability in susceptibility of bacteria for doxycycline, use of the product should be based on bacteriological sampling and susceptibility testing or recent experience on the farm.*

Amendments to the pharmacokinetic section of the SPC and the origin of the MIC values included in this section should be inserted, too.

The Applicant has given a full discussion on statistical analyses conducted for the pivotal trial. During the Mutual Recognition Procedure this statistical evaluation was questioned and found to be inappropriate. Therefore the applicant performed another statistical evaluation using the original database. The applicant felt that this was more adapted towards the Guideline EMEA/CVMP/816/00 and obtained greater clinical significance. A new primary end point was defined as **Time to clinical cure**, i.e. the time to absence of clinical signs.

New secondary end points were defined as **percentage clinically cured on day 7 relapse and mortality rates. Global evaluations were justified because the statistical guideline incorporates them.**

For **Time to clinical cure**, Doxyprex at 200ppm and at 300ppm groups were cured at 3.2 and 3.33 days respectively compared to the TM550 group at 8.2 days, the Stabox group at 11.75 days and the control group at 13.67 days. In two-by-two analysis, both Doxyprex groups were significantly quicker to cure than the negative control and the positive control groups. **Time to clinical cure** was considered the primary end point.

The CVMP concluded that according to “current” GCP requirements this pivotal study design has many deficiencies. This is in agreement with the German Competent National Authority (BVL) and expert opinion. However, the study was conducted and assessed prior to these requirements and the applicant has attempted many additional analyses on the original data and has justified various deficiencies. Although on the surface the individual numbers of pigs involved looks small, the applicant has justified that because of the large difference in results between the Doxyprex and control groups the small number of animals still allows a 80% power to be achieved. This should therefore be acceptable. All the results show a clear improvement of Doxyprex treated pigs, with no relapses and no deaths, compared to a negative control. To sum up the applicant has indeed performed a number of analyses based on the original data and they seem to have been performed appropriately.

Deficiencies in the pivotal clinical trial demonstrating efficacy of the product for the treatment of *P.multocida* and *B. bronchiseptica* were compensated for by a discussion of the field data in the literature reference provided. The applicant demonstrated through these references that the product fulfils the criteria for a well-established use application.

In conclusion the applicant has justified their application as well-established use of the active substance, doxycycline. The submitted references supported pharmacodynamics including MIC data (more than 5 years old) and pharmacokinetics of the active substance, doxycycline. In addition the pharmacokinetics study using their final formulation and more up-to-date (2001) MIC data for respiratory pathogens isolated from pigs in Spain are provided. The applicant submitted a target species tolerance study and post marketing pharmacovigilance data to support safety of the product. Resistance was covered adequately in literature. The applicant conducted a pivotal controlled, randomized two-centred field trial using their final formulation to demonstrate efficacy for respiratory disease caused by *P.multocida* and *B.bronchiseptica*. The submitted post marketing experience consists of:

- (1) Pharmacovigilance – reporting a nil return for suspected adverse drugs reactions and lack of efficacy; and
- (2) Five expert opinions written by veterinarians who work closely with large pigs farms in Spain, all containing positive comments on their use of this product. From all this information, a significant potential serious risk for safety or efficacy of Doxyprex, for the treatment or control of clinical signs of porcine respiratory disease caused by *P.multocida* and *B.bronchiseptica* cannot be identified.

2. For the second clinical study “ Efficacy of the doxycycline in feed for the control of pneumonia caused by *P. multocida* and *Mycoplasma hyopneumoniae*”

No dose confirmation studies appear to have been presented in this study and therefore it was important that the references provided should present robust evidence for the field efficacy of the product.

Pulmodox is indicated for prevention of clinical respiratory disease and not for treatment,

In order to establish that Doxyprex is similarly bioavailable to the product Pulmodox 5% Premix, the applicant referred to information from the SPC and the hevra.org website. It was pointed out that even though there are small differences in dosage the mean and maximum steady state plasma concentration are similar.

There are however differences in both dose recommendation (12.5 mg/kg/day versus 10 mg/kg/day) and duration of treatment (8 versus 7 days).

Based on this information the CVMP agreed that the provided references are not suitable as **pivotal** evidence of clinical efficacy of the product Doxyprex for the proposed indication and dose regimen for *M.Hyopneumoniae*

### **1. Conclusion and recommendation**

The CVMP recommendation is to grant the marketing authorisation to Doxyprex 100 mg/g Premix for medicated feeding stuff for pigs the following suggested indication because a positive risk:benefit analysis has been demonstrated and no potential serious risk has been identified.

“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.”

A risk:benefit analysis could not be conducted due to the lack of pivotal evidence on clinical efficacy for the indication *M. hyopneumoniae*. Therefore, the recommendation is to remove this pathogen from the indications.

**ANNEX III**

**SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE INSERT**



## **SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Doxyprex 100 mg/g Premix

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

### Active substance:

100 mg of Doxycycline base as  
hyclate

### Excipients:

Semoline q.s.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff  
Doxyprex is presented as 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 administer in animals with hypersensitivity to tetracyclines.  
Do not administer to animals with hepatic damage.

### 4.4. Special warnings

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. If it occurs, it is recommended to wash the area with plenty of water.

Do not smoke, eat or drink while handling the product.

If symptoms appear after exposition as a skin eruption, a doctor should be consulted showing these warnings. 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 antimicrobial agent should be adjusted taking into account the daily feed intake at the onset of treatment.

The following calculation can be used to calculate dosage:

$1 \text{ mg Doxyprex/kg feed} = 10 \text{ mg doxycycline/kg b.w.} \times 10 \times \text{bodyweight (kg)}/\text{Daily feed intake (kg)}$

Mixing instructions:

The premix is only intended to be incorporated into granulated medicated feeding stuffs.

The following complete feeding stuffs for pigs can be used for the manufacturing of medicated feeds:

Piglet starter feed I (complete feed up to approx. 20 kg body weight)

Piglet starter feed II (complete feed up to approx. 35 kg body weight)

Complete feed for fattening pigs up to approx. 50 kg body weight

Complete feed for fattening pigs of approx. 50 kg body weight

Complete feed for fattening pigs of approx. 35 kg body weight

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 55-65°C and 10% moisture. Before granulation, flour should not reach a temperature higher than 55 °C.

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

No symptoms of intolerance to the speciality 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<sub>90</sub> 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<sup>2+</sup> complex due to mutations in the chromosome. Cross-resistance is frequent between tetracyclines.

#### **5.2. Pharmacokinetic particulars**

Absorption after oral and intramuscular administration shows a high bioavailability. After oral administration, in most species values higher than 70% 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  $2.0 \pm 0.4$  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

Semolina (*declared on labelling as carrier*)

### **6.2. Incompatibilities**

Do not administer with oxidant substances.

### **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 pelleted feed: 3 months.

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

### **6.4. Special precautions for storage**

Store below 30 °C.

### **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**

Industrial Veterinaria, S.A.  
Esmeralda, 19  
E-08950 Esplugues de Llobregat (Barcelona) Spain  
Tel: +34 934 706 270  
Fax: +34 933 727 556  
e-mail: [invesa@invesagroup.com](mailto:invesa@invesagroup.com)

**8. MARKETING AUTHORISATION NUMBER(S)/ MRP PROCEDURE NUMBER**

**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.

**LABELLING AND PACKAGE INSERT**

## **PACKAGE LEAFLET**

### **Doxyprex 100 mg/g Premix**

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

Industrial Veterinaria, S.A.  
Esmeralda, 19  
E-08950 Esplugues de Llobregat (Barcelona) Spain

#### **2. NAME OF THE VETERINARY MEDICINAL PRODUCT**

Doxyprex 100 mg/g Premix

#### **3. STATEMENT OF THE ACTIVE SUBSTANCE AND OTHER INGREDIENTS**

Doxyprex is presented as yellow granules containing 100 mg of doxycycline base as hyclate per gram of product. Semoline is employed as carrier.

#### **4. INDICATION(S)**

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.

#### **5. CONTRAINDICATIONS**

Do not administer in animals with hypersensitivity to tetracyclines.  
Do not administer to animals with hepatic damage.

#### **6. ADVERSE REACTIONS**

Allergic reactions and photosensitivity may appear, as for all tetracyclines.  
Digestive alterations by intestinal dysbiosis may appear in very long-term treatments.  
If you notice any serious effects or other effects not mentioned in this label, please inform your veterinary surgeon.

#### **7. TARGET SPECIES**

Pigs (after weaning)

#### **8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION**

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 antimicrobial agent 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)

## **9. ADVICE ON CORRECT ADMINISTRATION**

Mixing instructions:

The premix is only intended to be incorporated into granulated medicated feeding stuffs.

The following complete feeding stuffs for pigs can be used for the manufacturing of medicated feeds:

Piglet starter feed I (complete feed up to approx. 20 kg body weight)

Piglet starter feed II (complete feed up to approx. 35 kg body weight)

Complete feed for fattening pigs up to approx. 50 kg body weight

Complete feed for fattening pigs of approx. 50 kg body weight

Complete feed for fattening pigs of approx. 35 kg body weight

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 55-65°C and 10% moisture. Before granulation, flour should not reach a temperature higher than 55 °C.

## **10. WITHDRAWAL PERIOD**

Meat and offal: 7 days.

## **11. SPECIAL STORAGE PRECAUTIONS**

Keep out of the reach and sight of children.

Store below 30 °C.

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

EXP {month/year}

Do not use after the expiry date.

Shelf-life after first opening the immediate packaging: 3 months.

Shelf-life after incorporation into pelleted feed: 3 months.

## **12. SPECIAL WARNING(S)**

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.

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.

Do not administer with oxidant substances.

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.

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.

Avoid skin and eye contact. If it occurs, it is recommended to wash the area with plenty of water. Do not smoke, eat or drink while handling the product. 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.

If symptoms appear after exposition as a skin eruption, a doctor should be consulted showing these warnings. Inflammation of the face, lips and eyes or respiratory difficulty are more severe signs that require urgent medical attention

It is not recommended its use in pregnant animals and during lactation periods.

### **13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY**

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

### **14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED**

{<DD/MM/YYYY>}

### **15. OTHER INFORMATION**

To be supplied only on veterinary prescription

#### **PACKAGE SIZE**

1 kg  
5 kg  
20 kg  
25 kg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE  
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE**

{NATURE/TYPE}

**1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

Doxyprex 100 mg/g Premix

**2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES**

Doxyprex is presented as yellow granules containing 100 mg of doxycycline base as hyclate per gram of product. Semoline is employed as carrier.

**3. PHARMACEUTICAL FORM**

Premix for medicated feeding stuff

**4. PACKAGE SIZE**

1 kg  
5 kg  
20 kg  
25 kg

**5. TARGET SPECIES**

Pigs (after weaning)

**6. INDICATION(S)**

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.

**7. METHOD AND ROUTE(S) OF ADMINISTRATION**

In feed use

**8. WITHDRAWAL PERIOD**

Meat and offal: 7 days.

## **9. SPECIAL WARNING(S), IF NECESSARY**

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.

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.  
Do not administer with oxidant substances.

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.

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.

Avoid skin and eye contact. If it occurs, it is recommended to wash the area with plenty of water.  
Do not smoke, eat or drink while handling the product.  
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.

If symptoms appear after exposition as a skin eruption, a doctor should be consulted showing these warnings. Inflammation of the face, lips and eyes or respiratory difficulty are more severe signs that require urgent medical attention

It is not recommended its use in pregnant animals and during lactation periods.

## **10. EXPIRY DATE**

## **11. SPECIAL STORAGE CONDITIONS**

Keep out of the reach and sight of children.  
Store below 30 °C.  
After first opening, keep the pack tightly closed. Store in a dry place.

EXP {month/year}

Do not use after the expiry date.

Shelf-life after first opening the immediate packaging: 3 months.

Shelf-life after incorporation into pelleted feed: 3 months.

## **12. SPECIFIC PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY**

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

**13. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable**

**14. THE WORDS “KEEP OUT OF THE REACH AND SIGHT OF CHILDREN”**

Keep out of the reach and sight of children.

**15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Industrial Veterinaria, S.A.  
Esmeralda, 19  
E-08950 Esplugues de Llobregat (Barcelona) Spain

**16. MARKETING AUTHORISATION NUMBER(S)**

**17. MANUFACTURER’S BATCH NUMBER**

Batch: {number}