Annex I

List of the names, pharmaceutical form(s), strength of the veterinary medicinal products, animal species, route of administration, applicant / marketing authorisation holder in the member states

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN & Strength	Pharmaceutical form	Animal species
Austria	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g Pulver zum Eingeben über das Trinkwasser für Hühner	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Chicken
Austria	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g Pulver zum Eingeben über das Trinkwasser für Schweine	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Pigs
Belgium	Eurovet N.V. Poorthoevestraat 4, 3 550 Heusen-Zolder Belgium	Soludox 50%	Doxycycline hyclate 500 mg/g	Water Soluble Powder for oral administration	Pigs Chickens
Czech Republic	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g prášek pro podání v pitné vodě pro prasata	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Pigs
Denmark	Eurovet Animal Health B.V., P.O. 179, Handelsweg 25, NL-5531 AE Bladel, The Netherlands	Soludox Vet.	Doxycycline hyclate 500 mg/g	Water Soluble Powder	Pigs
Estonia	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox, 500 mg/g, suukaudse lahuse pulber sigadele	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Pigs

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN & Strength	Pharmaceutical form	Animal species
Estonia	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox, 500 mg/g, suukaudse lahuse pulber kanadele	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Chickens
Finland	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g jauhe juomaveteen sekoitettavaksi sioille	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Pig
Finland	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g jauhe juomaveteen sekoitettavaksi kanoille	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Chicken
France	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 433 mg/g poudre pour administration dans l'eau de boisson pour poulets	Doxycycline (as hyclate) 433 mg/g	Powder for use in drinking water	Chicken
France	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 433 mg/g poudre pour administration dans l'eau de boisson pour porcs.	Doxycycline (as hyclate) 433 mg/g	Powder for use in drinking water	Pigs
Germany	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g Pulver zum Eingeben	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Chicken

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN & Strength	Pharmaceutical form	Animal species
Germany	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g Pulver zum Eingeben über das Trinkwasser für Schweine	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Pigs
Greece	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g κόνις για χρήση στο πόσιμο νερό για όρνιθες	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Chicken
Hungary	Eurovet Animal Health B.V., P.O. 179, Handelsweg 25, NL-5531 AE Bladel, The Netherlands	Soludox 50% pulvis A.U.V.	Doxycycline hyclate 500 mg/g	Powder for oral solution	Chicken
Italy	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g polvere per uso in acqua di bevanda per suini	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Pigs
Italy	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g polvere per uso in acqua di bevanda per polli.	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Chicken
Latvia	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g pulveris lietošanai ar dzeramo ūdeni cūkām	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Pigs

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN & Strength	Pharmaceutical form	Animal species
Latvia	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g pulveris lietošanai ar dzeramo ūdeni vistām	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Chicken
Lithuania	Eurovet Animal Health B.V. Handelsveg 25 - PO Box 179, 5530 AD Bladel The Netherlands	SOLUDOX 500 mg/g, geriamieji milteliai,	Doxycycline hyclate 500 mg/g	Powder for oral solution	Pigs and chicken
The Netherlands	Eurovet Animal Health B.V. Handelsveg 25 - PO Box 179, 5530 AD Bladel The Netherlands	DOXY ORT 50% Poeder voor toediening aan het drinkwater van varkens en kippen	Doxycycline hyclate 500 mg/g	Powder for administration in the drinking water	Pigs and non-egg laying chickens.
The Netherlands	Eurovet Animal Health B.V. Handelsveg 25 - PO Box 179, 5530 AD Bladel The Netherlands	DOXYFAR 50% Poeder voor toediening aan het drinkwater van varkens en kippen	Doxycycline hyclate 500 mg/g	Powder for administration in the drinking water	Pigs and non-egg laying chickens.
The Netherlands	Eurovet Animal Health B.V. Handelsveg 25 - PO Box 179 5530 AD Bladel The Netherlands	SOLUDOX 50%, poeder voor toediening via het drinkwater aan varkens en kippen	Doxycycline hyclate 500 mg/g	Powder for administration in the drinking water	Pigs and non-egg laying chickens.

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN & Strength	Pharmaceutical form	Animal species
The Netherlands	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg per gram voor gebruik in drinkwater voor kippen	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Chicken
Poland	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 50%; 500 mg/g proszek do podawania w wodzie do picia dla świń i kur	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	pigs, chickens (non-egg laying)
Slovakia	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g prášok pre užívanie s pitnou vodou pre ošípané	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Pigs
Spain	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g polvo para administración en agua de bebida para porcino	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Pigs
Spain	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g polvo para administración en agua de bebida para pollos.	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Chickens
UK	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox, 500 mg/g, Water Soluble Powder for Pigs	Doxycycline hyclate 500 mg/g	Water Soluble Powder	Pigs

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN & Strength	Pharmaceutical form	Animal species
UK	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g powder for use in drinking water for chickens	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Chickens
UK	Eurovet Animal Health B.V., Handelsweg 25, 5531 AE Bladel, The Netherlands	Soludox 500 mg/g powder for use in drinking water for pigs	Doxycycline hyclate 500 mg/g	Powder for use in drinking water	Pigs

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet

Overall summary of the scientific evaluation of Doxyfar 50% and associated names *(see annex I)*

1. Introduction

Doxyfar 50 % and associated names is a powder for use in drinking water containing the active substance doxycycline hyclate 500 mg/g. Doxycycline is a semi-synthetic tetracycline antibiotic. Tetracyclines have broad spectrum activity inhibiting Gram-positive and Gram-negative bacteria, *mycoplasmas*, *chlamydiae*, *rickettsias* and some *protozoa*. Doxycycline is bacteriostatic and acts by inhibiting protein synthesis intracellularly by binding to the 30-S subunit of the bacterial ribosome.

Due to the divergent national decisions taken by Member States concerning the authorisation of Doxyfar 50 % and associated names, the issue was referred to CVMP under Article 34(1) of Directive 2001/82/EC, in order to resolve divergences amongst the nationally authorised Summary of Product Characteristics (SPC) across the European Union.

The main sections of disharmony of the existing SPCs were:

- Target species;
- Indications;
- Amounts to be administered;
- Withdrawal periods.

It was noted that there have been no "real" divergent decisions taken by the Member States regarding the target species (chickens and pigs) because the Marketing Authorisation Holder's decisions for inclusion/exclusion of chickens and/or pigs as target species were based on commercial grounds and the data in support of the applications was the same.

2. Discussion of data available

Chickens

Data had previously been submitted as part of the recent Article 35 referral for all strengths of water soluble powders and oral solutions containing doxycycline hyclate indicated for use in poultry and intended for administration via the drinking water (EMEA/V/A/047). For the treatment of *P. multocida*, a dosage regimen of 10 mg/kg body weight for 4 or 5 days was agreed. For *O. rhinotracheale*, no therapeutic dose could be confirmed. In addition the Marketing Authorisation Holder submitted Periodic Safety Update Report (PSUR) data which indicated that no adverse events in chickens, including suspected lack of expected efficacy, has been reported for the past 5 years in the European Union. The Marketing Authorisation Holder provided persuasive argument that in the field differentiation between *Pasteurellosis* and *O. rhinotracheale* in poultry could be readily achieved. On the basis of well established use and absence of data for suspected lack of expected efficacy the dose regimen for infections caused by *P. multocida* of 10 mg doxycycline hyclate per kg body weight for 3 to 4 consecutive days and for infections caused by *O. rhinotracheale* of 20 mg doxycycline hyclate per kg body weight for 3 to 4 consecutive days were considered acceptable.

The chicken meat residue depletion data for both dosing regimens (10 mg doxycycline hyclate per kg body weight per day for 4 days and 20 mg doxycycline hyclate per kg body weight per day for 4 days) were submitted. A chicken meat withdrawal period of 3 days following a dose rate of 10 mg doxycycline hyclate per kg body weight per day for 4 days was considered acceptable. In addition

a chicken meat withdrawal period of 12 days following a dose rate of 20 mg doxycycline hyclate per kg body weight per day for 4 days was considered acceptable.

Pigs

There was no clear discrepancy between Member States in the dose regimen for use of the product in pigs.

The Marketing Authorisation Holder has provided evidence that the baseline PK of doxycycline, when delivered orally to pigs at a dose of 12.5 mg/kg body weight will provide plasma levels of 0.71 - 1.14 µg/ml (Pijpers *et al* (1991) [1]. Further the Marketing Authorisation Holder has also provided evidence (Bousquet *et al.* 1998)[2] that doxycycline will concentrate in nasal secretions and if fed at dose regimens between 11.8 -13.3 mg/kg body weight for 1 hour per day concentrations of between 0.7 and 1 µg/ml are achieved in the lung and nasal concentrations of 1.7 +/- 0.4 µg/ml are reached. If the same feed is provided *ad libitum* throughout the day the lung concentration rises to 2.9 +/- 0.6 µg/ml. Bousquet *et al.* 1997[3] provides evidence of minimum inhibitory concentrations (MICs) of doxycycline against: *P. multocida* of 0.13 - 2.0 µg/ml (55 strains), *A. pleuropneumoniae* 0.25 - 2.0 µg/ml (59 strains), *M. hyponeumoniae* 0.016 - 2 µg/ml (26 strains). Significantly no cross resistance was observed between oxytetracycline and doxycycline. From these data it may be predicted that doxycycline concentrations would exceed the MIC in the target tissue for the majority of the named pathogens in pigs.

The Marketing Authorisation Holder was requested to submit data to support the target species and indications in pigs. In response to this the Marketing Authorisation Holder submitted PSUR data covering the past 5 years. There have been no reports of adverse events in pigs, including suspected lack of expected efficacy, during the last 5 years.

The pig meat residue depletion data was made available and supported a meat withdrawal period of 4 days when pigs are administered 12.5 mg doxycycline hyclate/kg body weight/day for up to 8 days.

3. Benefit Risk assessment

Benefit Assessment

Chickens

No data have been provided for chickens, however the Marketing Authorisation Holder submitted in support of the recent Article 35 referral for all strengths of water soluble powders and oral solutions containing doxycycline hyclate indicated for use in poultry and intended for administration via the drinking water (EMEA/V/A/047).

It was agreed that the target species should be harmonised across all Member States where the product is authorised or pending authorisation and in consistency with the recent Article 35 harmonisation as "chickens (broiler, pullet, breeder)", and the following indications for Doxyfar 50% and associate names were agreed:

- Chickens (broiler, pullet, breeder): Where clinical disease is present in the flock, to reduce mortality, morbidity and clinical signs and to reduce lesions due to *Pasteurella multocida* or to reduce morbidity and lesions in respiratory infections caused by *O. rhinotracheale*.

[1] Pijpers, A. et al. (1991), Plasma levels of oxytetracycline, doxycycline, and monocycline in pigs after oral administration in feed. J. Amer. Sci. 69, 4512-4522
[2] Bousquet et al. 1998, Pharmacokinetics of doxycycline in pigs following oral administration in feed Vet.Res. 29 , 475-485
[3] Bousquet E., Morvan H., Aitken I., Morgan J.H.(1997), Comparative in vitro activity of doxycycline and oxytetracycline against porcine respiratory pathogens, Veterinary Record, July 12, 141(2), p. 37-40

At the time of the Article 35 referral, there was no documented evidence in relation to suspected lack of expected efficacy of doxycycline products in chickens. Data were provided in support of the indication for *P. multocida* at a dose of 10 mg doxycycline hyclate per kg body weight per day. Data were inconclusive with regards to the indication for *O. rhinotracheale*, but it was concluded that on the basis of well established use and as there have been no reports of adverse events, including suspected lack of expected efficacy, the current dosage could be considered to be safe and effective.

The following recommended dose for Doxyfar 50% and associate names was agreed:

- Chickens (broiler, pullet, breeder): 10 mg doxycycline hyclate per kg body weight per day for 3-4 days for the treatment of infections caused by *P. multocida* and 20 mg doxycycline hyclate per kg body weight per day for 3-4 days for the treatment of infections caused by *O. rhinotracheale*.

Residue depletion data in chickens support a meat withdrawal period of 3 days when chickens are administered at 10 mg doxycycline hyclate/kg body weight/day for 4 days.

Residue depletion data in chickens support a meat withdrawal period of 12 days when chickens are administered at 20 mg doxycycline hyclate/kg body weight/day for 4 days.

Pigs

The Marketing Authorisation Holder submitted a body of literature references which supported a prediction that when administered at the proposed dose rate, doxycycline concentration in the relevant tissues would exceed the MIC for most target pathogens. No further clinical trial or field trial data were submitted.

Published data related to existing levels of resistance to doxycycline in target pathogens was also submitted. The majority of the data quoted related to tetracycline resistance generally, and it was noted that resistance to doxycycline specifically was less commonly documented. There have been no data to indicate increasing levels of resistance and the relevance of cross resistance between doxycycline and older tetracyclines was also discussed but again data were insufficient to enable firm conclusions to be reached.

There have been no reports of adverse events, including suspected lack of expected efficacy of the product in pigs in the Periodic Safety Update Report data covering the period of the last 5 years. Doxycyline hyclate can be considered to have "well established use".

The following indications for Doxyfar 50% and associate names were agreed:

- Pigs: For the treatment of the clinical signs associated with porcine respiratory disease caused by *Actinobacillus pleuropeumoniae*, *Pasteurella multocida* and *Mycoplasma hyopneumoniae* susceptible to doxycycline.

The following recommended dose for Doxyfar 50% and associate names was agreed:

- Pigs: 12.5 mg doxycycline hyclate (25 mg product) per kg body weight per day for 4 consecutive days. If no improvement in clinical signs is seen within this time, the diagnosis should be reviewed and treatment changed. In case of severe infections the medication period may be prolonged for a maximum of 8 consecutive days as determined by the attending veterinary surgeon.

Residue depletion data in pigs support a meat withdrawal period of 4 days when pigs are administered at 12.5 mg doxycycline hyclate/kg body weight/day for up to 8 days.

Risk Assessment

Doxycycline is listed as a "highly important antimicrobial" for human use, and "critically important" for veterinary use according to the WHO criteria, 2007. In human medicine, doxycycline is the

treatment of choice for the treatment of acute tracheobronchitis, acute bronchitis and acute bronchiolitis caused by primary bacterial infections (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*) and bacterial superinfections (*Pneumococci*, *Haemophilus spp.*). Food-borne, direct as well as environmental transmission of resistant microorganisms (resistant determinants) has to be considered a risk related to the use of the product despite the fact that quantification of transmission of zoonotic agents and horizontal transfer of resistance genes between animal and human bacteria is extremely difficult *in vivo* (F. J. Angulo et al., 2004)[4]. It was identified at the time of the Article 35 referral for water soluble powders and oral solutions containing doxycycline hyclate that a high resistance rate to tetracyclines existed in *E. coli* isolated from chickens (De Jong et al, 2009)[5]. High levels of resistance to tetracyclines in swine respiratory pathogens have been documented (ARBAO-II study, 2008)[6]. Although resistance in the latter pathogens may be of less significance to public health, provision of an appropriate dosing regimen to limit the development of resistance is necessary to protect animal health.

In addressing the dosing regimen the Marketing Authorisation Holder has not discussed Pharmacokinetic/Pharmacodynamic in terms of a parameter that will limit the development of resistance. However, it is accepted that levels of resistance to tetracyclines reported in literature cannot be directly extrapolated to doxycycline, and that the greater liposolubility of doxycycline may explain why *in vitro* susceptibility of organisms has been maintained despite the emerging resistance to tetracycline. The lack of an epidemiologically based surveillance programme and standardised susceptibility testing methodology complicates interpretation of reports. In addition, in the absence of any adverse pharmacovigilance data indicating suspected lack of expected efficacy, it is considered that revision of the dose rate and regimen is not justified.

There are no changes to the dosing regimen being proposed for either chickens or pigs therefore there will be no increased exposure of the environment to doxycycline.

Risk management or mitigation measures

The precautions to limit the development of resistance, which were recommended by CVMP during the Article 35 referral, have been included in section 4.5 of the SPC. These warnings have been broadened to take account of resistance to tetracyclines recognised in isolates from pigs. Additional information has been added to the SPC regarding mechanisms of resistance to tetracyclines in general.

The chicken residue depletion data submitted allowed the setting of meat withdrawal periods in chickens. A chicken meat withdrawal period of 3 days when chickens are treated with 10 mg doxycycline hyclate/kg bw/day for 4 days; and a meat withdrawal period of 12 days when the chicken are treated with 20 mg doxycycline hyclate/kg bw/day for 4 days can be accepted.

When pigs are administered 12.5 mg doxycycline hyclate/kg bw/day for 8 days; meat withdrawal periods of 4 days will ensure consumer safety.

Evaluation of the Benefit-risk balance

It is clear that there are very limited scientific data available to support many of the proposed indications for use of the product, however it could be considered to have "well established use".

[4] F. J. Angulo et al., Evidence of an Association Between Use of Anti-microbial Agents in Food Animals and Anti-microbial Resistance Among Bacteria Isolated from Humans and the Human Health Consequences of Such Resistance, J. Vet. Med.. 51: 374 – 379

[5] De Jong et al.: A pan-European survey of antimicrobial susceptibility towards human-use antimicrobial drugs among zoonotic and commensal bacteria isolated from healthy food producing animals. J Antimicrob. Chemotherapy 63, 733-744,2009

[6] The ARBAO-II study, Occurrence of antimicrobial resistance among bacterial pathogens and indicator bacteria in pigs in different European countries form year 2002-2004, Acta Veterinaria Scandinavica 50(19) (2008)

In addition, no evidence from pharmacovigilance of serious risk has been demonstrated to be associated with the current dosing regimens for chickens or pigs and as such they can be maintained.

General warnings and advice relating to antimicrobial resistance have been strengthened.

The final conclusion for the benefit-risk balance for the use of the product remains positive.

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas:

- the CVMP considered that the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet;
- the CVMP reviewed the summary of products characteristics, labelling and package leaflet proposed by the marketing authorisation holder and considered all the overall submitted data;

the CVMP recommends the variation of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Doxyfar 50 % and associated names *(see Annex I)*.

Annex III

Summary of product characteristics, labelling and package leaflet

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Soludox 500 mg/g powder for use in drinking water for pigs and chickens
Soludox 433 mg/g powder for use in drinking water for pigs and chickens (France only)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 gram of powder contains:

Active substance:
Doxycycline hyclate 500 mg, corresponding to 433 mg doxycycline
France: Doxycycline 433 mg, corresponding to 500 mg doxycycline hyclate

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

3 PHARMACEUTICAL FORM

Powder for use in drinking water
Yellow crystalline powder

4 CLINICAL PARTICULARS

4.1 Target species

Pigs and chickens (broiler, pullet, breeder).

4.2 Indications for use, specifying the target species

Pigs: For the treatment of the clinical signs associated with porcine respiratory disease caused by *Actinobacillus pleuropneumoniae, Pasteurella multocida,* and *Mycoplasma hyopneumoniae* susceptible to doxycycline.
Chickens: Where clinical disease is present in the flock, to reduce mortality, morbidity, and clinical signs and to reduce lesions due to Pasteurellosis caused by *Pasteurella multocida* or to reduce morbidity and lesions in respiratory infections caused by *Ornithobacterium rhinotracheale (ORT).*

4.3 Contra-indications

Do not use in case of hypersensitivity to the active substance or to any of excipients.
Do not use in animals with an impaired liver function.

4.4 Special warning for each target species.

None.

4.5 Special precautions for use

Special precautions for use in animals
Due to likely variability (time, geographical) in susceptibility of bacteria for doxycycline, especially susceptibility of *A. pleuropneumoniae* and *O. rhinotracheale* may differ from country to country and even farm to farm, bacteriological sampling and susceptibility testing are recommended. Use of the product should be based on culture and sensitivity of micro-organisms from diseased cases on farm. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.

As eradication of the target pathogens may not be achieved, medication should therefore be combined with good management practices, e.g. good hygiene, proper ventilation, no overstocking.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
If you know you are allergic to the tetracycline class of antibiotics, special care should be taken when handling this product or the medicated solution.
During preparation and administration of the medicated drinking water, skin contact with the product and inhalation of dust particles should be avoided. Wear impermeable gloves (e.g. rubber or latex) and an appropriate dust mask (e.g. disposable half-mask respirator conforming to European Standard EN149) when applying the product.
In the event of eye or skin contact, rinse the affected area with large amounts of clean water and if irritation occurs, seek medical attention. Wash hands and contaminated skin immediately after handling the product.
If you develop symptoms following exposure such as skin rash, you should seek medical advice and show this warning to the physician. Swelling of the face, lips or eyes, or difficulty with breathing are more serious symptoms and require urgent medical attention.
Do not smoke, eat or drink while handling the product.
Take measures to avoid producing dust when incorporating the product into water. Avoid direct contact with skin and eyes when handling the product to prevent sensitisation and contact dermatitis.

4.6 Adverse reactions (frequency and seriousness)

Tetracyclines may - in very rare cases - induce photosensitivity and allergic reactions. If suspected adverse reactions occur, treatment should be discontinued. Inform your veterinary surgeon if adverse reactions occur that are not stated.

4.7 Use during pregnancy, lactation or lay

Doxycycline has a low affinity for forming complexes with calcium and studies have demonstrated that doxycycline scarcely affects skeleton formation. No negative effects were observed in poultry after the administration of therapeutic doses of doxycycline.
In the absence of specific studies the use of the product is not recommended during pregnancy or lactation.

4.8 Interaction with other medicinal products and other forms of interaction

Do not combine with antibiotics that are bacteriocidal e.g. penicillins or cephalosporins.
Absorption of doxycycline can be decreased in the presence of high quantities of calcium, iron, magnesium or aluminium in the diet. Do not administered together with antacids, kaolin and iron preparations.
It is advised that the interval between the administration of other products containing polyvalent cations should be 1-2 hours because they limit the absorption of tetracyclines.
Doxycycline increases the action of anticoagulants.
The solubility of the product is pH dependent and will precipitate if mixed in alkaline solution.
Do not store the drinking water in metallic containers.

4.9 Amounts to be administered and administration route

Administration orally with the drinking water.

The recommended dose in pigs is:
12.5 mg doxycycline hyclate (25 mg product) per kg body weight per day for 4 consecutive days. If no improvement in clinical signs is seen within this time, the diagnosis should be reviewed and treatment changed. In case of severe infections the medication period may be prolonged for a maximum of 8 consecutive days as determined by the attending veterinary surgeon.

The recommended dose in chickens is:

10 mg doxycycline hyclate (20 mg product) per kg body weight per day for 3-4 consecutive days in case of infections caused by *P. multocida* and
20 mg doxycycline hyclate (40 mg product) per kg body weight per day for 3-4 consecutive days in case of infections caused by *O. rhinotracheale.*

Based on the dose to be used, and the number and weight of the animals to be treated, the exact daily amount of product can be calculated. The following formula can be used to calculate the concentration of the product in drinking water:

$$\frac{\text{mg product / kg body weight / day} \times \text{Mean body weight (kg) of animals to be treated}}{\text{Mean daily water consumption (l) per animal}} = \text{.... mg product per l drinking water}$$

To ensure a correct dosage body weight should be determined as accurately as possible. The uptake of medicated drinking water depends on the clinical condition of the pigs/chickens. In order to obtain the correct dosage the concentration of doxycycline has to be adjusted accordingly. The use of suitably calibrated weighing equipment is recommended if part packs are used. The daily amount is to be added to the drinking water such that all medication will be consumed in 24 hours. Medicated drinking water should be refreshed or replaced every 24 hours. It is recommended to prepare a concentrated pre-solution - approximately 100 grams product per litre drinking water - and to dilute this further to therapeutic concentrations if required. Alternatively, the concentrated solution can be used in a proportional water medicator. Solubility of the product is pH dependent and it may precipitate if it is mixed in hard alkaline drinking water. Use at minimum concentrations of 200 mg powder per litre drinking water in areas with hard alkaline drinking water (hardness above 10.2 °d and pH more than 8.1). During the treatment period animals should not have access to other water sources than the medicated water.

4.10 Overdose (symptoms, emergency procedures, antidotes)

Overdoses up to 1.6 times the label recommended dose resulted in no clinical signs that could be attributed to treatment. Poultry tolerate double overdoses of doxycycline (40 mg/kg body weight) without any clinical effect.

4.11 Withdrawal periods

Pigs:
- Meat and offal: 4 days

Chickens:
- Meat and offal: 3 days, following a dose rate of 10 mg/kg body weight for 4 days.
- Meat and offal: 12 days, following a dose rate of 20 mg/kg body weight for 4 days.
- Eggs: Not authorised for use in laying birds producing eggs for human consumption. Do not use within 4 weeks of onset of the laying period

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterial - Tetracycline. ATC vet code: QJ 01 AA 02

5.1 Pharmacodynamic properties

Doxycycline belongs to the group of the tetracycline antibiotics. These antibiotics have a broad spectrum of antimicrobial activity, sharing the same basic structure of polycyclic naphthacenecarboxamide.
Doxycycline is primarily a bacteriostatic drug. It exerts its action by inhibiting the protein synthesis of the bacterial cell. Inhibition of bacterial protein synthesis results in disturbance of all functions

necessary for the life of bacteria. Especially cell-division and the formation of the cell wall are impaired.
Doxycycline is a broad-spectrum antibiotic, active against a large number of Gram-positive and Gram-negative, aerobe and anaerobe micro-organisms, Mycoplasmata, Chlamydiae and Rickettsia.
For *Ornithobacterium* rhinotracheale results demonstrate a great variation from high to low susceptibility, depending on the geographical region where isolates came from.
In pig pathogens resistance against doxycycline may also vary; especially susceptibility figures of *A. pleuropneumoniae* may differ from country to country and even farm to farm.
Four resistance mechanisms acquired by microorganisms against tetracyclines in general have been reported: Decreased accumulation of tetracyclines (decreased permeability of the bacterial cell wall and active efflux), protein protection of the bacterial ribosome, enzymatic inactivation of the antibiotic and rRNA mutations (preventing the tetracycline binding to ribosome). Tetracycline resistance is usually acquired by means of plasmids or other mobile elements (e.g. conjugative transposones). Cross resistance between tetracyclines has also been described. Due to the greater liposolubility and greater facility to pass through cell membranes (in comparison to tetracycline), doxycycline retains a certain degree of efficacy against microorganisms with acquired resistance to tetracyclines.

5.2 Pharmacokinetic properties

Doxycycline is absorbed in the stomach and the first part of the duodenum. Compared to the older tetracyclines the absorption of doxycycline is less affected by the presence of bivalent cations in food. Bioavailability in non-fasted pigs is approximately 21%.
Following oral administration at a dose of 12.8 mg/kg body weight, steady state concentrations during medication range between a C_{min} of 0.40 µg/ml in the early morning to a C_{max} of 0.87 µg/ml in the late afternoon in pigs.
Following administration of doxycycline hyclate at an actual dose of 21 mg/kg body weight to chickens mean plasma concentrations above 1 µg/ml were reached within 6 hours and lasted for 6 hours after cessation of medication. From 24 h up to 96 h after start of treatment the doxycycline plasma concentrations exceeded 2 µg/ml. Following administration of doxycycline hyclate at an actual dose of 10 mg/kg body weight steady state plasma concentrations ranged from 0.75 to 0.93 µg/g between 12 and 96 hours after start of medication.
Because doxycycline is highly lipid soluble, it has a good tissue penetration. Respiratory tract tissue: plasma ratios of 1.3 (healthy lungs), 1.9 (pneumonic lungs) and 2.3 (nasal mucosa) have been reported for doxycycline. Plasma protein binding is high (over 90%).
Doxycycline is scarcely metabolised. Doxycycline is primarily excreted with the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tartaric acid

6.2 Incompatibilities

Solubility of doxycycline is pH dependent. Precipitation will occur in an alkaline solution. In the absence of compatibility studies, this 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: 9 months

Shelf-life after dilution or reconstitution according to directions: After reconstitution with water, any product remaining after 24 hours should be discarded.

6.4 Storage precautions

This veterinary medicinal product does not require any special storage conditions.
Keep the bag tightly closed after first opening in order to protect from moisture.

6.5 Nature and composition of immediate packaging

Sachets of 100g, 250g, 500g and 1 kg and 10x 100g in a carton box.
Formed from a polyester/polyethylene/aluminium/polyethylene or a polyester/ polyethylene/aluminium/ionomer laminate.
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

To be completed nationally

8. MARKETING AUTHORISATION NUMBER

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

To be completed nationally

PROHIBITION OF SALE, SUPPLY AND/OR USE

To be completed nationally

LABEL TEXT
<u>SINGLE</u> SACHETS/BAGS

1x 100g/250g/500g/1kg

The full text will be printed on the <u>single</u> sachet/bag
Format used is especially for this type of labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGE
=
IMMEDIATE PACKAGE
=
LEAFLET

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Soludox 500 mg/g powder for use in drinking water for pigs and chickens
Doxycycline hyclate
France only: Soludox 433 mg/g powder for use in drinking water for pigs and chickens
Doxycycline

2. STATEMENT OF THE ACTIVE SUBSTANCE AND OTHER INGREDIENT

Composition per gram product

Active Substance:	
Doxycycline hyclate	500 mg corresponding to 433 mg doxycycline
France: Doxycycline	*433 mg corresponding to 500 mg doxycycline hyclate*
Excipients	
Tartaric acid	500 mg

3. PHARMACEUTICAL FORM

Yellow powder for use in drinking water.

4. PACKAGE SIZE

100 g *(250 g, 500 g, 1 kg)*

5. TARGET SPECIES

Pigs and chickens (broiler, pullet, breeder).

6. INDICATION(S)

Pigs: For the treatment of the clinical signs associated with porcine respiratory disease caused by *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Mycoplasma hyopneumoniae* susceptible to doxycycline.
Chickens: Where clinical disease is present in the flock, to reduce mortality, morbidity, and clinical signs and to reduce lesions due to Pasteurellosis caused by *Pasteurella multocida* or to reduce morbidity and lesions in respiratory infections caused by *Ornithobacterium rhinotracheale (ORT).*

7. CONTRAINDICATIONS

Do not use in case of hypersensitivity to the active substance or to any of excipients.
Do not use in animals with an impaired liver function.

8. ADVERSE REACTIONS

Tetracyclines may - in very rare cases - induce photosensitivity and allergic reactions. If suspected adverse reactions occur, treatment should be discontinued. If you notice any serious effects or other effects not mentioned in this product information, please inform your veterinary surgeon or pharmacist.

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

Administration orally with the drinking water.
The recommended dose in pigs is:
12.5 mg doxycycline hyclate (25 mg product) per kg body weight per day for 4 consecutive days. If no improvement in clinical signs is seen within this time, the diagnosis should be reviewed and treatment changed. In case of severe infections the medication period may be prolonged for a maximum of 8 consecutive days as determined by the attending veterinary surgeon.
The recommended dose in chickens is:
10 mg doxycycline hyclate (20 mg product) per kg body weight per day for 3-4 consecutive days in case of infections caused by *P. multocida* and
20 mg doxycycline hyclate (40 mg product) per kg body weight per day for 3-4 consecutive days in case of infections caused by *O. rhinotracheale*
Based on the dose to be used, and the number and weight of the animals to be treated, the exact daily amount of product can be calculated. The following formula can be used to calculate the concentration of the product in drinking water:

$$\frac{\text{mg product / kg body weight / day} \times \text{Mean body weight (kg) of animals to be treated}}{\text{Mean daily water consumption (l) per animal}} = \text{.... mg product per l drinking water}$$

To ensure a correct dosage body weight should be determined as accurately as possible. The uptake of medicated drinking water depends on the clinical condition of the pigs/chickens. In order to obtain the correct dosage the concentration of doxycycline has to be adjusted accordingly. The use of suitably calibrated weighing equipment is recommended if part packs are used. The daily amount is to be added to the drinking water such that all medication will be consumed in 24 hours. Medicated drinking water should be refreshed or replaced every 24 hours. It is recommended to prepare a concentrated pre-solution - approximately 100 grams product per litre drinking water - and to dilute this further to therapeutic concentrations if required. Alternatively, the concentrated solution can be used in a proportional water medicator. Solubility of the product is pH dependent and it may precipitate if it is mixed in hard alkaline drinking water. Use at minimum concentrations of 200 mg powder per litre drinking water in areas with hard alkaline drinking water (hardness above 10.2 °d and pH more than 8.1). During the treatment period animals should not have access to other water sources than the medicated water.

10. WITHDRAWAL PERIODS

Pigs:
- Meat and offal: 4 days

Chickens:
- Meat and offal: 3 days, following a dose rate of 10 mg/kg body weight for 4 days.
- Meat and offal: 12 days, following a dose rate of 20 mg/kg body weight for 4 days.
- Eggs: Not authorised for use in laying birds producing eggs for human consumption.
Do not use within 4 weeks of onset of the laying period.

11. SPECIAL WARNINGS

Special precautions for use in animals
Due to likely variability (time, geographical) in susceptibility of bacteria for doxycycline, especially susceptibility of *A. pleuropneumoniae* and *O. rhinotracheale* may differ from country to country and even farm to farm, bacteriological sampling and susceptibility testing are recommended. Use of the product should be based on culture and sensitivity of micro-organisms from diseased cases on farm. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.
As eradication of the target pathogens may not be achieved, medication should therefore be combined with good management practices, e.g. good hygiene, proper ventilation, no overstocking.

User warnings
If you know you are allergic to the tetracycline class of antibiotics, special care should be taken when handling this product or the medicated solution.
During preparation and administration of the medicated drinking water, skin contact with the product and inhalation of dust particles should be avoided. Wear impermeable gloves (e.g. rubber or latex) and an appropriate dust mask (e.g. disposable half-mask respirator conforming to European Standard EN149) when applying the product.
In the event of eye or skin contact, rinse the affected area with large amounts of clean water and if irritation occurs, seek medical attention. Wash hands and contaminated skin immediately after handling the product.
If you develop symptoms following exposure such as skin rash, you should seek medical advice and show this warning to the physician. Swelling of the face, lips or eyes, or difficulty with breathing are more serious symptoms and require urgent medical attention.
Do not smoke, eat or drink while handling the product.
Take measures to avoid producing dust when incorporating the product into water. Avoid direct contact with skin and eyes when handling the product to prevent sensitisation and contact dermatitis.

Use during pregnancy or lactation
Doxycycline has a low affinity for forming complexes with calcium and studies have demonstrated that doxycycline scarcely affects skeleton formation. No negative effects were observed in poultry after the administration of therapeutic doses of doxycycline.
In the absence of specific studies the use of the product is not recommended during pregnancy or lactation.

Interactions with other medicinal products and other forms of interaction
Do not combine with antibiotics that are bactericidal like penicillins or cephalosporins.
Absorption of doxycycline can be decreased in the presence of high quantities of calcium, iron, magnesium or aluminium in the diet. Do not administered together with antacids, kaolin and iron preparations.
It is advised that the interval between the administration of other products containing polyvalent cations should be 1-2 hours because they limit the absorption of tetracyclines.
Doxycycline increases the action of anticoagulants.
The solubility of the product is pH dependent and will precipitate if mixed in alkaline solution.
Do not store the drinking water in metallic containers.
In the absence of compatibility studies, this product must not be mixed with other veterinary medicinal products.

12. EXPIRY DATE

EXP {month/year}; Do not use after the expiry date stated on the label after EXP.

13. SPECIAL STORAGE PRECAUTIONS

This veterinary medicinal product does not require any special storage conditions.
Keep the bag tightly closed after first opening in order to protect from moisture.
Shelf-life after first opening the packaging: 9 months.
Shelf-life after dilution or reconstitution according to directions: After reconstitution with water any product remaining after 24 hours should be discarded.

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

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

15. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only.
Prescription only medicine - To be completed nationally.

16. THE WORDS "KEEP OUT OF THE REACH AND SIGHT OF CHILDREN"

Keep out of the reach and sight of children.

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

To be completed nationally

18. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

19. MANUFACTURER'S BATCH NUMBER

Lot {number}

20. DATE ON WHICH THE TEXT WAS LAST APPROVED

To be completed nationally

21. OTHER INFORMATION

Pack sizes: 100g, 10x 100g, 250g, 500g and 1 kg
Not all pack sizes may be marketed.

LABELLING 10 x 100 g

Carton box for the 10x100 grams Alufoil sachets
with label for 100 gram sachets
and leaflet

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARTON 10 X 100 GRAM only

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Soludox 500 mg/g powder for use in drinking water for pigs and chickens
Doxycycline hyclate
France only: Soludox 433 mg/g powder for use in drinking water for pigs and chickens
Doxycycline

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Composition per gram product:

Active Substance:	
Doxycycline hyclate	500 mg corresponding to 433 mg doxycycline
France: Doxycycline	*433 mg corresponding to 500 mg doxycycline hyclate*
Excipients	
Tartaric acid	500 mg

3. PHARMACEUTICAL FORM

Yellow powder for use in drinking water.

4. PACKAGE SIZE

10x100 gram

5. TARGET SPECIES

Pigs and chickens (broiler, pullet, breeder).

6. INDICATION(S)

Pigs: For the treatment of the clinical signs associated with porcine respiratory disease caused by *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Mycoplasma hyopneumoniae* susceptible to doxycycline.
Chickens: Where clinical disease is present in the flock, to reduce mortality, morbidity, and clinical signs and to reduce lesions due to Pasteurellosis caused by *Pasteurella multocida* or to reduce morbidity and lesions in respiratory infections caused by *Ornithobacterium rhinotracheale (ORT)*.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

To be administered orally in the drinking water.

8. WITHDRAWAL PERIOD

Pigs:
- Meat and offal: 4 days

Chickens:
- Meat and offal: 3 days, following a dose rate of 10 mg/kg body weight for 4 days.
- Meat and offal: 12 days, following a dose rate of 20 mg/kg body weight for 4 days.
- Eggs: Not authorised for use in laying birds producing eggs for human consumption.
Do not use within 4 weeks of onset of the laying period.

9. SPECIAL WARNING(S), IF NECESSARY

Special precautions for use in animals
Read the package leaflet before use.

User Warnings
Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}; Do not use after the expiry date stated on the label after EXP.

11. SPECIAL STORAGE CONDITIONS

This veterinary medicinal product does not require any special storage conditions.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Any unused veterinary medicinal product or waste material 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

For animal treatment only.
Prescription only medicine *(or similar wording, national issue)*

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

To be completed nationally

16. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

17. MANUFACTURER'S BATCH NUMBER

Lot{number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Aluminium Foil Sachet 100g (packed per 10)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Soludox 500 mg/g powder for use in drinking water for pigs and chickens
Doxycycline hyclate
France only: Soludox 433 mg/g powder for use in drinking water for pigs and chickens
Doxycycline

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Composition per gram product:

Active Substance:	
Doxycycline hyclate	500 mg corresponding to 433 mg doxycycline
France: Doxycycline	*433 mg corresponding to 500 mg doxycycline hyclate*
Excipients	
Tartaric acid	500 mg

3. PHARMACEUTICAL FORM

Yellow crystalline powder for use in drinking water.

4. PACKAGE SIZE

100 gram

5. TARGET SPECIES

Pigs and chickens (broiler, pullet, breeder).

6. INDICATION(S)

Pigs: For the treatment of the clinical signs associated with porcine respiratory disease caused by *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Mycoplasma hyopneumoniae* susceptible to doxycycline.
Chickens: Where clinical disease is present in the flock, to reduce mortality, morbidity, and clinical signs and to reduce lesions due to Pasteurellosis caused by *Pasteurella multocida* or to reduce morbidity and lesions in respiratory infections caused by *Ornithobacterium rhinotracheale (ORT)*.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

To be administered orally in the drinking water.

8. WITHDRAWAL PERIOD

Pigs:
- Meat and offal: 4 days

Chickens:
- Meat and offal: 3 days, following a dose rate of 10 mg/kg body weight for 4 days.
- Meat and offal: 12 days, following a dose rate of 20 mg/kg body weight for 4 days.
- Eggs: Not authorised for use in laying birds producing eggs for human consumption.
Do not use within 4 weeks of onset of the laying period.

9. SPECIAL WARNING(S), IF NECESSARY

Special precautions for use in animals
Read the package leaflet before use.

User Warnings:
Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}; Do not use after the expiry date stated on the label after EXP.

11. SPECIAL STORAGE CONDITIONS

This veterinary medicinal product does not require any special storage conditions.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Any unused veterinary medicinal product or waste material 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

For animal treatment only.
Prescription only medicine *(or similar wording, national issue)*

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

To be completed nationally

16. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

17. MANUFACTURER'S BATCH NUMBER

Lot{number}

PACKAGE LEAFLET

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

To be completed nationally

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Soludox 500 mg/g powder for use in drinking water for pigs and chickens
Doxycycline hyclate.
France only: Soludox 433 mg/g powder for use in drinking water for pigs and chickens
Doxycycline.

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

Composition per gram product:

Active Substance:	
Doxycycline hyclate	500 mg corresponding to 433 mg doxycycline
France: Doxycycline	*433 mg corresponding to 500 mg doxycycline hyclate*
Excipients	
Tartaric acid	500 mg

4. INDICATION(S)

Pigs: For the treatment of the clinical signs associated with porcine respiratory disease caused by *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Mycoplasma hyopneumoniae* susceptible to doxycycline.
Chickens: Where clinical disease is present in the flock, to reduce mortality, morbidity, and clinical signs and to reduce lesions due to Pasteurellosis caused by *Pasteurella multocida* or to reduce morbidity and lesions in respiratory infections caused by *Ornithobacterium rhinotracheale (ORT)*.

5. CONTRAINDICATIONS

Do not use in case of hypersensitivity to the active substance or to any of excipients.
Do not use in animals with an impaired liver function.

6. ADVERSE REACTIONS

Tetracyclines may - in very rare cases - induce photosensitivity and allergic reactions. If suspected adverse reactions occur, treatment should be discontinued. If you notice any serious effects or other effects not mentioned in this product information, please inform your veterinary surgeon or pharmacist.

7. TARGET SPECIES

Pigs and chickens (broiler, pullet, breeder).

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

Administration orally with the drinking water.
The recommended dose in pigs is:
12.5 mg doxycycline hyclate (25 mg product) per kg body weight per day for 4 consecutive days. If no improvement in clinical signs is seen within this time, the diagnosis should be reviewed and treatment changed. In case of severe infections the medication period may be prolonged for a maximum of 8 consecutive days as determined by the attending veterinary surgeon.
The recommended dose in chickens is:
10 mg doxycycline hyclate (20 mg product) per kg body weight per day for 3-4 consecutive days in case of infections caused by *P. multocida* and
20 mg doxycycline hyclate (40 mg product) per kg body weight per day for 3-4 consecutive days in case of infections caused by *O. rhinotracheale*

9. ADVICE ON CORRECT ADMINISTRATION

Based on the dose to be used, and the number and weight of the animals to be treated, the exact daily amount of product can be calculated. The following formula can be used to calculate the concentration of the product in drinking water:

$$\frac{\text{mg product / kg body weight / day} \times \text{Mean body weight (kg) of animals to be treated}}{\text{Mean daily water consumption (l) per animal}} = \text{.... mg product per l drinking water}$$

To ensure a correct dosage body weight should be determined as accurately as possible. The uptake of medicated drinking water depends on the clinical condition of the pigs/chickens. In order to obtain the correct dosage the concentration of doxycycline has to be adjusted accordingly. The use of suitably calibrated weighing equipment is recommended if part packs are used. The daily amount is to be added to the drinking water such that all medication will be consumed in 24 hours. Medicated drinking water should be refreshed or replaced every 24 hours. It is recommended to prepare a concentrated pre-solution - approximately 100 grams product per litre drinking water - and to dilute this further to therapeutic concentrations if required. Alternatively, the concentrated solution can be used in a proportional water medicator. Solubility of the product is pH dependent and it may precipitate if it is mixed in hard alkaline drinking water. Use at minimum concentrations of 200 mg powder per litre drinking water in areas with hard alkaline drinking water (hardness above 10.2 °d and pH more than 8.1). During the treatment period animals should not have access to other water sources than the medicated water.

10. WITHDRAWAL PERIOD

Pigs:
- Meat and offal: 4 days

Chickens:
- Meat and offal: 3 days, following a dose rate of 10 mg/kg body weight for 4 days.
- Meat and offal: 12 days, following a dose rate of 20 mg/kg body weight for 4 days.
- Eggs: Not authorised for use in laying birds producing eggs for human consumption.

Do not use within 4 weeks of onset of the laying period.

11. SPECIAL STORAGE PRECAUTIONS

This veterinary medicinal product does not require any special storage conditions.
Keep the bag tightly closed after first opening in order to protect from moisture.
Shelf-life after first opening the packaging: 9 months.

Shelf-life after dilution or reconstitution according to directions: After reconstitution with water any product remaining after 24 hours should be discarded.

12. SPECIAL WARNING(S)

Special precautions for use

(i) Special precautions for use in animals
Due to likely variability (time, geographical) in susceptibility of bacteria for doxycycline, especially susceptibility of *A. pleuropneumoniae* and *O. rhinotracheale* may differ from country to country and even farm to farm, bacteriological sampling and susceptibility testing are recommended. Use of the product should be based on culture and sensitivity of micro-organisms from diseased cases on farm. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.
As eradication of the target pathogens may not be achieved, medication should therefore be combined with good management practices, e.g. good hygiene, proper ventilation, no overstocking.

(ii) User warnings:
If you know you are allergic to the tetracycline class of antibiotics, special care should be taken when handling this product or the medicated solution.
During preparation and administration of the medicated drinking water, skin contact with the product and inhalation of dust particles should be avoided. Wear impermeable gloves (e.g. rubber or latex) and an appropriate dust mask (e.g. disposable half-mask respirator conforming to European Standard EN149) when applying the product.
In the event of eye or skin contact, rinse the affected area with large amounts of clean water and if irritation occurs, seek medical attention. Wash hands and contaminated skin immediately after handling the product.
If you develop symptoms following exposure such as skin rash, you should seek medical advice and show this warning to the physician. Swelling of the face, lips or eyes, or difficulty with breathing are more serious symptoms and require urgent medical attention.
Do not smoke, eat or drink while handling the product.
Take measures to avoid producing dust when incorporating the product into water. Avoid direct contact with skin and eyes when handling the product to prevent sensitisation and contact dermatitis.

Use during pregnancy or lactation
Doxycycline has a low affinity for forming complexes with calcium and studies have demonstrated that doxycycline scarcely affects skeleton formation. No negative effects were observed in poultry after the administration of therapeutic doses of doxycycline.
In the absence of specific studies the use of the product is not recommended during pregnancy or lactation.

Interactions with other medicinal products and other forms of interaction
Do not combine with antibiotics that are bactericidal like penicillins or cephalosporins.
Absorption of doxycycline can be decreased in the presence of high quantities of calcium, iron, magnesium or aluminium in the diet. Do not administered together with antacids, kaolin and iron preparations.
It is advised that the interval between the administration of other products containing polyvalent cations should be 1-2 hours because they limit the absorption of tetracyclines.
Doxycycline increases the action of anticoagulants.
The solubility of the product is pH dependent and will precipitate if mixed in alkaline solution.
Do not store the drinking water in metallic containers.
In the absence of compatibility studies, this product must not be mixed with other veterinary medicinal products.

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

Any unused veterinary medicinal product or waste material 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

To be completed nationally

15. OTHER INFORMATION

Pack sizes: 100g, 10x100g, 250g, 500g and 1 kg
Not all pack sizes may be marketed.