

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
Belgium	Dopharma Research BV Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Doxycycline 50% Dopharma	Doxycycline hyclate 500 mg/g	Water Soluble Powder	Non-ruminating calves Pigs Non-laying poultry
Bulgaria	Dopharma B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Doxycycline 50% WSP	Doxycycline hyclate 500 mg/g	Water Soluble Powder	Calves, pigs, poultry
Denmark	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Doxylin Vet.	Doxycycline hyclate 500 mg/g	Water Soluble Powder	Pigs
Greece	Dopharma B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Doxycycline 50% Dopharma	Doxycycline hyclate 500 mg/g	Water Soluble Powder	Chickens (broilers) Calves Pigs
Hungary	Dopharma B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Doxycycline 50% WSP	Doxycycline hyclate 500 mg/g	Powder for oral solution	Calves, pigs, chicken
Lithuania	Dopharma B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Doxycycline 50%	Doxycycline hyclate 500 mg/g	Powder for oral solution	Calves, pigs and poultry

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN & Strength	Pharmaceutical form	Animal species
The Netherlands	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Doxycycline 50% WSP	Doxycycline hyclate 500 mg/g	Powder for administration in drinking water	Non-egg laying chickens
Poland	Dopharma B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	DoxyMed 50	Doxycycline hyclate 500 mg/g	Water Soluble Powder	Calves, chicken, pigs
Portugal	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Vetadoxi 50	Doxycycline hyclate 500 mg/g	Water Soluble Powder	Cattle (calves), swine, birds
Romania	Dopharma B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Doxycycline 50% WSP	Doxycycline hyclate 500 mg/g	Water Soluble Powder	Poultry (not for use in animals from which eggs are produced for human consumption) Calves Pig

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 Doxycycline 50% WSP and associated names (see annex I)

1. Introduction

Doxycycline 50% WSP 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*.

Due to the divergent national decisions taken by Member States concerning the authorisation of Doxycycline 50 % WSP 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.

2. Discussion of data available

Poultry

No Minimum Inhibitory Concentration (MIC) data were submitted that were specifically relevant to isolates from target pathogens from chickens. A pharmacokinetics study demonstrated that when Doxycycline 50% WSP was administered in drinking water to broilers at a dose of doxycycline hyclate of 25 mg/kg body weight/day for 5 days, a steady state plasma doxycycline concentration of 2 µg/ml was reached after 6 hours. Data from Goren, 1983¹, on the *in vitro* susceptibility of pathogens isolated from poultry between 1978 and 1981 showed that susceptibility of *P. multocida* was > 70%, but that of *E. coli* varied between 4 to 34% over the time period studied. A study investigated the safety of Doxycycline 50% WSP administered at doses of 0, 25 and 75 mg doxycycline hyclate/kg body weight /day for 5 days. No health abnormalities were detected.

Two literature references reported that doxycycline at 50 mg per litre in drinking water for 3 - 5 days was effective in treating challenge infections with *E. coli* (George, 1977²) and *E. coli* and *M. gallisepticum* (Migaki, 1977³). In a study by Goren, 1988⁴, using a challenge infection with an *E. coli* strain with an MIC of 1 µg/ml, a dose related therapeutic effect was demonstrated, with moderate to good effects noticed in groups receiving doxycycline doses of 96 to 196 mg/kg body weight/day, which gave plasma concentrations of 1.7 to 3.6 µg/ml. A Good Clinical Practice standard field study was provided investigating the efficacy of Doxycycline 50% WSP to treat naturally occurring outbreaks of colibacillosis on 5 farms in The Netherlands in 1998. This was an uncontrolled study and poultry houses where *E. coli* strains were found not to be susceptible to

¹ Goren E., Treatment of Infectious Disease Due to Bacteria in Commercial Poultry, Tijdschr. Diergeneesk. d., deet Iûs, afl. 9 (1983)

² George et al, Comparison of therapeutic efficacy of doxycycline, chlortetracycline and lincomycin-spectinomycin on *E. coli* infection of young chickens. Poultry Sci. 56, 452-458 (1977)

³ Migaki et al, Efficacy of doxycycline against experimental complicated chronic respiratory disease compared with commercially available water medicants in broilers Poultry Sci. 56, 1739 (1977)

⁴ Goren et al, Therapeutic efficacy of doxycycline hyclate in experimental *Escherichia coli* infection in broilers, The Vet Quarterly, 10,48-52 (1988)

doxycycline on *in vitro* testing were excluded. A dose of doxycycline hyclate of 25 mg/kg body weight/day in drinking water for 3 days produced decreased mortalities and resolution of clinical signs on all farms except one by the end of treatment. The study highlighted the importance of susceptibility testing prior to treatment with doxycycline.

No data were submitted in relation to *Haemophilus paragallinarum*, *Bordetella avium* and *Clostridia spp* infections.

The pharmacovigilance data (summary of Periodic Safety Update Reports (PSURs)) from use of the product in chickens covering the past 5 years has been reviewed under 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 (EMA/V/A/047). There have been no adverse events in chickens, including suspected lack of expected efficacy reports during this period.

The chicken meat residue depletion data available support a meat withdrawal period of 5 days when chicken are administered 25 mg doxycycline hyclate/kg body weight/day for 5 days.

No data were provided in relation to poultry species other than chickens.

Pigs

MIC data from literature for porcine respiratory tract pathogens isolated from clinical cases in the Netherlands were provided (Pijpers, 1990⁵). The MIC90s values ranged from 0.03 µg/ml for *Mycoplasma hyopneumoniae* to 0.5 µg/ml for *P. multocida*. A dose finding study by Pijpers, 1990b⁶, investigated the prophylactic effect of doxycycline in feed against challenge with *Actinobacillus pleuropneumoniae*. In this study, doses of doxycycline equivalent to 16, 7.5 and 3.6 mg/kg body weight/day were effective in preventing disease in 6/6, 5/6 and 1/6 pigs, respectively. In the group treated with doxycycline at 16 mg/kg body weight/day, plasma levels were between 1.28 and 1.83 µg/ml, and exceeded the MIC of the challenge strain (1 µg/ml). A pharmacokinetic and residues study showed that at a daily dose of 10 mg doxycycline hydrochloride/kg body weight, doxycycline reached a steady state concentration of 0.4 µg/ml within 3 days. Pijpers, 1990, determined the steady-state concentration of doxycycline following oral in-feed administration at doses of 7, 13 and 26 mg/kg/body weight, twice daily. Steady state plasma levels for doxycycline ranged from 0.37 – 0.89 µg/ml (at 7 mg/kg body weight), 0.7 to 1.14 µg/ml (at 13 mg/kg body weight) and 1.62 to 3.18 µg/ml (at 26 mg/kg body weight). Although not submitted by the marketing authorisation holder, information from the ARBAO-II⁷ project reporting on the occurrence of antimicrobial resistance among bacteria causing infections in pigs in the European Union between 2002-2004 showed levels of resistance to tetracyclines in *Actinobacillus pleuropneumoniae* between 0 and 46.0% and in *Strep. suis* between 48.0 and 92.0%. It was accepted that this level of resistance could not be directly extrapolated to doxycycline. A study investigated the safety of Doxycycline 50% WSP administered at dose rates of 0, 10, 50 and 150 mg doxycycline hyclate/kg body weight/day for 10 days. Administration at up to 5 X Recommended Treatment Dose was well tolerated.

No clinical data were submitted to support use of Doxycycline 50% WSP in the treatment of atrophic rhinitis or bronchopneumonia.

No field trial data were submitted to support the use of the product in pigs.

⁵ Pijpers A., Plasma levels of oxytetracycline, doxycycline and minocycline in pigs after oral administration in feed, Feed Medication with Tetracyclines in Pigs, 85-103 (1990)

⁶ Pijpers A., Prophylaxis of pleuropneumonia by doxycycline in-feed medication in pigs, Feed Medication with Tetracyclines in Pigs, 125-143 (1990)

⁷ The ARBAO-II study, Occurrence of antimicrobial resistance among bacterial pathogens and indicator bacteria in pigs in different European countries from year 2002-2004, Acta Veterinaria Scandinavica 50(19) (2008)

Pharmacovigilance data (summary of PSURs) from use of the product in pigs have been provided covering the past 5 years. There have been no adverse events in pigs, including suspected lack of expected efficacy reports during this period.

The pig meat residue depletion data available support a meat withdrawal period of 8 days when pigs are administered 10 mg doxycycline hyclate/kg body weight/day for 5 days.

Calves

No MIC data were submitted that were specifically relevant to isolates from target pathogens from calves. A pharmacokinetic and residues study showed that at a daily dose of 10 mg doxycycline hydrochloride/kg body weight, administered once daily via milk replacer for 5 days, C_{max} was achieved within 2 - 3 days with a mean value of 2.2 to 2.5 µg/ml. In a study by Meijer, 1993⁸, following administration of doxycycline hyclate at 5 mg/kg body weight/twice daily via milk replacer for 5 days to immature calves, plasma concentrations varied between 1.0 and 2.3 µg/ml. Kremer, 1988⁹ and Hartman, 1993¹⁰ & 1994¹¹ showed high levels of resistance in *Pasteurella spp* isolated from veal calves in the Netherlands. A study showed that Doxycycline hyclaat 50% was well tolerated when administered at the recommended dose of 5 mg doxycycline hyclate/kg body weight/ twice daily for twice the recommended duration (10 days). However, administration at 5 X and 10 X Recommended Treatment Dose was not well tolerated with animals showing anorexia, diarrhoea and evidence of renal failure necessitating euthanasia.

A summary of field trial data (Van Gool, 1986¹²) provided evidence of efficacy of Ronaxan P.S. 5% (doxycycline hyclate) administered in milk replacer at a dose of 10 mg/kg body weight/ day for 4 - 6 days in the treatment of calves suffering from pneumonia caused by *Mycoplasma* and *Past. haemolytica*. Treatment was considered to have been effective in 98% of calves treated with Ronaxan (n=361) compared to 85% of calves treated with reference antimicrobial products (n=174). A study by Kuttler, 1978¹³ showed that doxycycline was effective in moderating anaplasmosis in splenectomised calves infected with *Anaplasma marginale*.

No clinical or field data have been presented to support use of the product in the treatment of pleuropneumonia (*Histophilus somni*) or bronchopneumonia involving *H. somni*, *P. multocida*, *Streptococcus spp* or *Arcanobacterium pyogenes*.

The calf meat residues depletion data available support a meat withdrawal period of 7 days when calves are administered 5 mg doxycycline hyclate/kg body weight twice a day for 5 days.

Pharmacovigilance data (summary of PSURs) from use of the product in calves were provided covering the past 5 years. There have been no adverse events in calves, including suspected lack of expected efficacy reports during this period.

⁸ Meijer et al, Pharmacokinetics and bioavailability of doxycycline hyclate after oral administration in calves, Vet. Quart. 15 (1)1 1-5 (1993)

⁹ Kremer et al, Resistentiepatronen van enkele uit vlees- en fokkalveren geïsoleerde bacteriën, Tijdschr. Diergeneeskd., 113 (23), 1298-1302 (1988)

¹⁰ Hartman, E.G., Antibioticgevoeligheid van bacteriën geïsoleerd door de gezondheidsdiensten in Nederland in 1991, Tijdschr. Diergeneeskd., 118 (6), 193-195 (1993)

¹¹ Hartman, E.G., Antibioticgevoeligheid van bacteriën geïsoleerd door de gezondheidsdiensten voor dieren in Nederland in 1992, Tijdschr. Diergeneeskd., 119 (1), 17 (1994)

¹² Gool et al, Caracteristiques pharmacocinetiques et bilan des essais cliniques pour le traitement ou la metaphylaxe des bronchopneumonies infectieuses des veaux par le roxanan, Proc. 14th World Congr. Dis. Cattle, 627-631 (1986)

¹³ Kuttler et al, Relative efficacy of two oxytetracycline formulations and doxycycline in the treatment of acute anaplasmosis in splenectomized calves, Am. J. Vet. Res., 39 (2), 347-349 (1978)

3. Benefit Risk assessment

Benefit Assessment

Chickens

As no data have been provided for species of poultry other than chickens, it was agreed that the target species should be restricted to "chickens" across all Member States where the product is authorised or pending authorisation. In consistency with 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 (EMA/V/A/047), the following indications can be agreed:

- Infections of the respiratory tract caused by *Mycoplasma spp.*, *Escherichia coli*, *Haemophilus paragallinarium* and *Bordetella avium*.
- Enteritis caused by *Clostridium perfringens* and *Clostridium colinum*.

Data for some indications were absent, however, 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. In the absence of data supporting the dose regimen for infections other than colibacillosis, the harmonised dose regimen of 25 mg doxycycline hyclate/kg body weight for 3 to 5 days, for all indications can be accepted as this is the higher end of the dose range that has been historically used and poses no risk for safety.

Residue depletion data in chickens support a meat withdrawal period of 5 days when chicken are administered at 25 mg doxycycline hyclate/kg body weight/day for 5 days.

Pigs

As pigs are a target species on all current SPCs (except for the product in the Netherlands), it was agreed that target species "pigs" can be accepted in the harmonised product information. There have been no major discrepancies across the Member States in the following indications:

- Atrophic rhinitis caused by *Pasteurella multocida* and *Bordetella bronchiseptica*
- Bronchopneumonia caused by *Pasteurella multocida*, *Streptococcus suis* and *Mycoplasma hyorhinis*
- Pleuropneumonia caused by *Actinobacillus pleuropneumoniae*.

Limited clinical data were provided to support use of the product to treat pleuropneumonia caused by *A. pleuropneumoniae*, and no clinical or field data were provided to support use of doxycycline in the treatment of atrophic rhinitis or bronchopneumonia in pigs. There was no clear discrepancy between Member States in the dose regimen of 10 mg doxycycline hyclate/kg body weight for 3 to 5 days. Although the data provided suggested that that this dose might not be optimal and there is recent literature evidence for resistance development in swine respiratory pathogens to tetracyclines, there was no clear evidence upon which to base a revision of the dose/indications. The summary of PSURs data indicated no safety concerns or suspected lack of expected efficacy in relation to this indication or dose duration.

Residue depletion data in pigs support a meat withdrawal period of 8 days when pigs are administered at 10 mg doxycycline hyclate/kg body weight/day for 5 days.

Calves

Calves are a target species on all current SPCs (except for the product in the Netherlands). It was agreed that the target species should be clarified to be "pre-ruminant calves" in the harmonised

product information. There have been no discrepancies across the Member States in the following indications:

- Bronchopneumonia and pleuropneumonia caused by *Pasteurella spp.*, *Streptococcus spp.*, *Arcanobacterium pyogenes*, *Histophilus somni* and *Mycoplasma spp.*

Some field data were presented to support use of the product in the treatment of pneumonia caused by *Mycoplasma* and *P. haemolytica* in calves, but there were no clinical or field data to support use of the product in the treatment of pleuropneumonia (*H. somni*) or bronchopneumonia involving *H. somni*, *P. multocida*, *Streptococcus spp* or *A. pyogenes*. The summary of PSURs data indicated no safety concerns or suspected lack of expected efficacy in relation to this indication or dose duration. Considering all factors there was insufficient evidence to justify an alteration in the dose rate or regimen.

Residue depletion data in calves support a meat withdrawal period of 7 days when calves are administered at 5 mg doxycycline hyclate/kg body weight, twice a day for 5 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)¹⁴. 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)¹⁵. High levels of resistance to tetracyclines in swine respiratory pathogens have also been documented (ARBAO-II study, 2008)⁷. Appropriate definition of indications giving the users of the product clear information on the expected efficacy, together with appropriate dosing for the indications is necessary in order to ensure effective and safe use of the product in the field.

As data on calves presented in the dossier to support clinical data concern pre-ruminant calves, with a non clear rumen maturity for some studies presented in the dossier, and considering changes to the key pharmacokinetic parameters after i.v. administration in non-ruminating vs. ruminating calves and the fact that there is no clear margin of safety that might allow for review of the daily dose in calves, the target species should be clearly stated to be pre-ruminating calves.

There are no proposals to alter the dose regimen for chickens, pigs and calves thus the exposure of the environment to doxycycline will not increase. The use of the product as proposed is not expected to pose a risk for the environment.

Risk management or mitigation measures

The precautions recommended by the CVMP to limit the development of resistance, which resulted from 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 and

¹⁴ 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

¹⁵ 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

calves. Additional information has been added to the SPC regarding mechanisms of resistance to tetracyclines in general.

In order to help to ensure optimal bioavailability in the field, a warning has been included in section 4.8 of the SPC regarding the potential for doxycycline to chelate cations.

When chickens are administered a dose of 25 mg doxycycline hyclate/kg bw/day for 5 days; pigs are administered 10 mg doxycycline hyclate/kg bw/day for 5 days; and calves are administered 5 mg doxycycline hyclate/kg bw, twice a day for 5 days; meat withdrawal periods of 5, 8 and 7 days respectively, will ensure consumer safety.

To ensure that the product is only used in young calves prior to rumination being established, the target species has been updated to read "pre-ruminant calves."

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".

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

In view of the weaknesses in the existing data, the indications have been made more precise and SPC warnings and advice related 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 has recommended the variation of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Doxycycline 50% WSP and associated names (*see Annex I*).

Annex III

Summary of product characteristics, labelling and package leaflet

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per gram:

Active substance:

Doxycycline hyclate: 500 mg
(equivalent to 433 mg doxycycline)

Excipients:

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral solution.

Slightly yellowish powder.

4. CLINICAL PARTICULARS

4.1 Target species

Pre-ruminant calves, pigs, chickens.

4.2 Indications for use, specifying the target species

Treatment of the following specified infections of the respiratory tract and the alimentary tract caused by micro-organisms susceptible to doxycycline.

Pre-ruminant calves:

- Bronchopneumonia and pleuropneumonia caused by *Pasteurella spp.*, *Streptococcus spp.*, *Arcanobacterium pyogenes*, *Histophilus somni* and *Mycoplasma spp.*

Pigs:

- Atrophic rhinitis caused by *Pasteurella multocida* and *Bordetella bronchiseptica*;
- Bronchopneumonia caused by *Pasteurella multocida*, *Streptococcus suis* and *Mycoplasma hyorhinis*;
- Pleuropneumonia caused by *Actinobacillus pleuropneumoniae*.

Chickens:

- Infections of the respiratory tract caused by *Mycoplasma spp.*, *Escherichia coli*, *Haemophilus paragallinarum* and *Bordetella avium*;
- Enteritis caused by *Clostridium perfringens* and *Clostridium colinum*.

4.3 Contraindications

Do not use in case of hypersensitivity to tetracyclines or to any of the excipients.
Do not administer to animals with severe liver- or kidney insufficiency.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

Due to variability (time, geographical) in susceptibility of bacteria for doxycycline, bacteriological sampling and susceptibility testing of micro-organisms from diseased animals on farm are highly recommended.

A high resistance rate of *E. coli*, isolated from chickens, against tetracyclines has been documented. Therefore the product should be used for the treatment of infections caused by *E. coli* only after susceptibility testing has been carried out. Resistance to tetracyclines has also been reported in pig respiratory pathogens (*A. pleuropneumoniae*, *S. suis*) and calf pathogens (*Pasteurella spp*) in some EU countries.

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

During the handling of the product, skin contact and inhalation has to be avoided, taking into account the risk of sensitization and contact dermatitis. For that purpose wear gloves and a dust mask.

4.6 Adverse reactions (frequency and seriousness)

None known.

4.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:

Due to deposit of doxycycline in young bone tissue, use of the product should be limited during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interaction

Do not use in conjunction with bactericidal antibiotics, such as penicillins and cephalosporins. Tetracyclines can chelate cations (e.g. Mg, Mn, Fe and Al) and this may lead to decreased bioavailability

4.9 Amounts to be administered and administration route

To be administered orally through the milk-replacer and/or the drinking water.

Pre-ruminant calves: 10 mg doxycycline hyclate /kg body weight / day,
corresponding to 20 mg of product per kg body weight,
for 3-5 consecutive days, divided over 2 administrations.

Pigs: 10 mg doxycycline hyclate /kg body weight / day,
corresponding to 20 mg of product per kg body weight,
for 3-5 consecutive days.

Chickens: 25 mg doxycycline hyclate /kg body weight / day,
corresponding to 50 mg of product per kg body weight,
for 3-5 consecutive days.

For the administration through the drinking water, the exact daily amount of product should be calculated, based on the recommended dose, and the number and weight of the animals to be treated, according to the following formula:

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

To ensure a correct dosage body weight should be determined as accurately as possible. The uptake of medicated water is dependant on the clinical conditions of the animals. In order to obtain the correct dosage, the concentration in drinking water may have to be adjusted. 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 freshly prepared 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. The medicated milk replacer should be used immediately.

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

In calves acute, sometimes fatal myocardial degeneration can occur following single or multiple dosages. Since mostly this is caused by overdosage, it is important to measure the dosage accurately.

4.11 Withdrawal period

Meat and offal:
Calves: 7 days
Pigs: 8 days
Chickens: 5 days

Not permitted for use in laying birds producing eggs for human consumption.
Not permitted for use in cattle producing milk for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterial for systemic use, tetracyclines
ATCvet-code: QJ01AA02

5.1 Pharmacodynamic properties

Doxycycline is a broad spectrum antibiotic. It inhibits bacterial protein synthesis intracellularly by binding on the 30-S ribosome subunits. This interferes with binding of aminoacyl-tRNA to the acceptor site on the mRNA ribosome complex and prevents coupling of amino acids to the elongating peptide chains.

Doxycycline inhibits bacteria, Mycoplasma, Chlamydia, Rickettsia, and certain Protozoa.

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 quickly and almost completely absorbed from the intestine. The presence of food in the intestine has no effect on the actual absorption of doxycycline. The distribution of doxycycline and penetration of doxycycline throughout most body tissues is good.

Following absorption, tetracyclines are hardly metabolized. In contrast to the other tetracyclines, doxycycline is mainly excreted via the faeces.

Calves

After a dosage of 10 mg/kg body weight /day during 5 days, an elimination halftime varying between 15 and 28 hours was found. The doxycycline plasma level reached an average of 2.2 to 2.5 µg/ml.

Pigs

In pigs, no accumulation of doxycycline in plasma was found after treatment via the drinking water. Mean plasma values of 0.44 ± 0.12 µg/ml after 3 days of medication with an average dose of 10 mg/kg body weight were found.

Poultry

Steady state plasma concentrations of 2.05 ± 0.47 µg/ml were reached within 6 hours after start of the medication and varied between 1.28 and 2.18 µg/ml with a dosage of 25 mg/kg body weight during 5 days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid
Lactose

6.2 Incompatibilities

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

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 36 months.
Shelf life after first opening of the immediate packaging: 3 months.
Shelf life after reconstitution in drinking water: 24 hours.
Shelf life after reconstitution in milk replacer: use immediately.

6.4 Special precautions for storage

Store below 25 °C.
Do not refrigerate or freeze.
Protect from frost.

6.5 Nature and composition of immediate packaging

White polypropylene container of 1000 g, covered with a low-density polyethylene lid.

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

Any unused product or waste material should be disposed of in accordance with national requirements.

7. MARKETING AUTHORISATION HOLDER

Dopharma Research B.V.
Zalmweg 24
4941 VX Raamsdonksveer
The Netherlands
research@dopharma.com

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF THE 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

Not applicable.

LABELLING

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

PP Container

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally

2. STATEMENT OF THE ACTIVE AND OTHER SUBSTANCES

Doxycycline hyclate 500 mg/g
(equivalent to doxycycline 433 mg/g)

3. PHARMACEUTICAL FORM

Powder for oral solution.

4. PACKAGE SIZE

1 kg.

5. TARGET SPECIES

Pre-ruminant calves, pigs and chickens

6. INDICATION

Treatment of the following specified infections of the respiratory tract and the alimentary tract caused by micro-organisms susceptible to doxycycline.

Pre-ruminant calves:

- Bronchopneumonia and pleuropneumonia caused by *Pasteurella spp.*, *Streptococcus spp.*, *Arcanobacterium pyogenes*, *Histophilus somni* and *Mycoplasma spp.*

Pigs:

- Atrophic rhinitis caused by *Pasteurella multocida* and *Bordetella bronchiseptica*;
- Bronchopneumonia caused by *Pasteurella multocida*, *Streptococcus suis* and *Mycoplasma hyorhinis*;
- Pleuropneumonia caused by *Actinobacillus pleuropneumoniae*.

Chickens:

- Infections of the respiratory tract caused by *Mycoplasma spp.*, *Escherichia coli*, *Haemophilus paragallinarum* and *Bordetella avium*;
- Enteritis caused by *Clostridium perfringens* and *Clostridium colinum*.

7. METHOD AND ROUTE OF ADMINISTRATION

Oral use, after dissolution in drinking water/milk replacer.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Meat and offal:

Calves: 7 days

Pigs: 8 days

Chickens: 5 days

Not permitted for use in laying birds producing eggs for human consumption.

Not permitted for use in cattle producing milk for human consumption.

9. SPECIAL WARNING(S)

Read the package leaflet before use.

10. EXPIRY DATE

Exp <<EXP month/year>>

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

Shelf life after reconstitution in drinking water: 24 hours.

Shelf life after reconstitution in milk replacer: use immediately.

Once opened, use by:

11. SPECIAL STORAGE CONDITIONS

Store below 25 °C.

Do not refrigerate or freeze.

Protect from frost.

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

Any unused product or waste material should be disposed of in accordance with national requirements.

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

For animal treatment only - to be supplied only on veterinary prescription.

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

Dopharma Research B.V.
Zalmweg 24
4941 VX Raamsdonksveer
The Netherlands

16. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

17. MANUFACTURER'S BATCH NUMBER

Batch <<number>>

PACKAGE LEAFLET

PACKAGE LEAFLET

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

Marketing authorisation holder:

Dopharma Research B.V.
Zalmweg 24
4941 VX Raamsdonksveer
The Netherlands

Manufacturer responsible for the batch release:

Dopharma B.V.
Zalmweg 24
4941 VX Raamsdonksveer
The Netherlands

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally

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

Active substance:

Doxycycline hyclate 500 mg/g
(equivalent to doxycycline 433 mg/g)

Slightly yellowish powder.

4. INDICATION

Treatment of the following specified infections of the respiratory tract and the alimentary tract caused by micro-organisms susceptible to doxycycline.

Pre-ruminant calves:

- Bronchopneumonia and pleuropneumonia caused by *Pasteurella spp.*, *Streptococcus spp.*, *Arcanobacterium pyogenes*, *Histophilus somni* and *Mycoplasma spp.*.

Pigs:

- Atrophic rhinitis caused by *Pasteurella multocida* and *Bordetella bronchiseptica*;
- Bronchopneumonia caused by *Pasteurella multocida*, *Streptococcus suis* and *Mycoplasma hyorhinis*;
- Pleuropneumonia caused by *Actinobacillus pleuropneumoniae*.

Chickens:

- Infections of the respiratory tract caused by *Mycoplasma spp.*, *Escherichia coli*, *Haemophilus paragallinarum* and *Bordetella avium*;
- Enteritis caused by *Clostridium perfringens* and *Clostridium colinum*.

5. CONTRAINDICATIONS

Do not use in case of hypersensitivity to tetracyclines or any of the excipients.
Do not administer to animals with severe liver- or kidney insufficiency.

6. ADVERSE REACTIONS

None known.

If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Pre-ruminant calves, pigs, chickens

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

Pre-ruminant calves: 10 mg doxycycline hyclate /kg body weight / day, corresponding to 20 mg of product per kg body weight, for 3-5 consecutive days, divided over 2 administrations.

Pigs: 10 mg doxycycline hyclate /kg body weight / day, corresponding to 20 mg of product per kg body weight, for 3-5 consecutive days.

Chickens: 25 mg doxycycline hyclate /kg body weight / day, corresponding to 50 mg of product per kg body weight, for 3-5 consecutive days.

To be administered orally through the milk-replacer and/or the drinking water.

9. ADVICE ON CORRECT ADMINISTRATION

For the administration through the drinking water, the exact daily amount of product should be calculated, based on the recommended dose, and the number and weight of the animals to be treated, according to the following formula:

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

To ensure a correct dosage body weight should be determined as accurately as possible.

The uptake of medicated water is dependant on the clinical conditions of the animals. In order to obtain the correct dosage, the concentration in drinking water may have to be adjusted.

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 freshly prepared 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.

The medicated milk replacer should be used immediately.

10. WITHDRAWAL PERIOD

Meat and offal:

Calves: 7 days

Pigs: 8 days

Chickens: 5 days

Not permitted for use in laying birds producing eggs for human consumption.
Not permitted for use in cattle producing milk for human consumption.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the reach and sight of children.

Store below 25°C.

Do not refrigerate or freeze.

Protect from frost.

Do not use after the expiry date stated on the label after exp.

Shelf life after first opening the container: 3 months.

Shelf life after reconstitution in drinking water: 24 hours.

Shelf life after reconstitution in milk replacer: use immediately.

12. SPECIAL WARNINGS

Special precautions for use in animals

Due to variability (time, geographical) in susceptibility of bacteria for doxycycline, bacteriological sampling and susceptibility testing of micro-organisms from diseased animals on farm are highly recommended.

A high resistance rate of *E. coli*, isolated from chickens, against tetracyclines has been documented. Therefore the product should be used for the treatment of infections caused by *E. coli* only after susceptibility testing has been carried out. Resistance to tetracyclines has also been reported in pig respiratory pathogens (*A. pleuropneumoniae*, *S. suis*,) and calf pathogens (*Pasteurella spp*) in some EU countries.

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

During the handling of the product, skin contact and inhalation has to be avoided, taking into account the risk of sensitisation and contact dermatitis. For that purpose wear gloves and a dust mask.

Use during pregnancy, lactation or lay

Due to deposit of doxycycline in young bone tissue, use of the product should be limited during pregnancy and lactation.

Interactions with other medicinal products and other forms of interaction

Do not use in conjunction with bactericidal antibiotics, such as penicillins and cephalosporins. Tetracyclines can chelate cations (e.g. Mg, Mn, Fe and Al) and this may lead to decreased bioavailability.

Overdose (symptoms, emergency procedures, antidotes)

In calves acute, sometimes fatal myocardial degeneration can occur following single or multiple dosages. Since mostly this is caused by overdosage, it is important to measure the dosage accurately.

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

Any unused product or waste material should be disposed of in accordance with national requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

To be completed nationally

15. OTHER INFORMATION

To be completed nationally