# Annex I

# List of the name, pharmaceutical form, strength of the veterinary medicinal product, animal species, route of administration, marketing authorisation holder in the Member States

| Member State EU / EEA | Marketing authorisation holder | Name | INN | Pharmaceutical form | Strength | Animal species | Route of administration |
|---|---|---|---|---|---|---|---|
| Austria | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Soludox 500 mg/g Pulver zum Eingeben über das Trinkwasser für Schweine und Hühner | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |
| Czech Republic | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Soludox 500 mg/g prášek pro podání v pitné vodě pro prasata | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |
| Estonia | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Soludox 500 mg/g suukaudse lahuse pulber sigadele ja kanadele | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |
| Finland | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Soludox 500 mg/g jauhe juomaveteen sekoitettavaksi sioille ja kanoille | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |
| France | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Soludox 433 mg/g poudre pour administration dans l'eau de boisson des porcs et des poulets | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |
| Germany | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Soludox 500 mg/g Pulver zum Eingeben über das Trinkwasser für Schweine und Hühner | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |
| Greece | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Soludox 500 mg/g υπό μορφή σκόνης για χρήση σε πόσιμο νερό για χοίρους και κοτόπουλα | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |

| Member State EU / EEA | Marketing authorisation holder | Name | INN | Pharmaceutical form | Strength | Animal species | Route of administration |
|---|---|---|---|---|---|---|---|
| Italy | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Soludox 500 mg/g polvere da somministrare nell'acqua da bere per suini e polli | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |
| Italy | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Acquadox 500 mg/g polvere da somministrare nell'acqua da bere per suini e polli | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |
| Latvia | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Soludox 500 mg/g pulveris lietošanai ar dzeramo ūdeni cūkām un vistām | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |
| The Netherlands | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Soludox 500 mg/g poeder voor toediening via het drinkwater voor varkens en kippen | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |
| Slovakia | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Soludox 500 mg/g prášok na použitie v pitnej vode pre ošípané | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |
| Spain | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Soludox 500 mg/g polvo para administración en agua de bebida para porcino y pollos | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |
| United Kingdom | Eurovet Animal Health BV<br>Handelsweg 25<br>5531 AE Bladel<br>The Netherlands | Soludox 500 mg/g powder for use in drinking water for pigs and chickens | doxycycline hyclate | Powder for use in drinking water | 500 mg/g | Pigs and chickens | Oral: In drinking water |

# Annex II

# Scientific conclusions and grounds for the variation to the terms of the marketing authorisations

# Overall summary of the scientific evaluation of Soludox 500 mg/g powder for use in drinking water for pigs and chickens and associated names *(see annex I)*

## 1. Introduction

Soludox 500 mg/g powder for use in drinking water for pigs and chickens and associated names (see annex I) contains doxycycline hyclate as active ingredient. It is indicated in chickens 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*. There are two authorised dosages: 10 mg/kg body weight for 4 consecutive days, for which the withdrawal period is 3 days, and 20 mg/kg body weight for 4 consecutive days for which the withdrawal period is 12 days.

The marketing authorisation holder (MAH) Eurovet Animal Health BV, submitted an application for a type II variation to shorten the withdrawal period for chicken meat and offal at a dose rate of 20 mg/kg body weight for 4 consecutive days. The type II variation has been subject to a worksharing procedure (UK/V/xxxx/WS/006) by the veterinary Coordination Group for Mutual Recognition and Decentralised Procedures (CMD(v)) according to Article 20 of Commission Regulation (EC) No 1234/2008 involving Soludox 500 mg/g powder for use in drinking water for pigs and chickens (NL/V/0141/001/DC) and Soludox 500 mg/g powder for use in drinking water for pigs and chickens (UK/V/0349/001/DC). The application was submitted to the United Kingdom as reference Member State and to Austria, Czech Republic, Estonia, Finland, France, Germany, Greece, Italy, Latvia, the Netherlands, Slovakia and Spain as concerned Member States. The worksharing procedure started on 6 January 2012.

During the worksharing procedure a potential serious risk to human health was identified by the Netherlands regarding the appropriate withdrawal period for chicken meat and offal at a dose rate of 20 mg/kg body weight for 4 consecutive days.

This issue remained unsolved and therefore a CMD(v) procedure under Article 13(2) of Commission Regulation (EC) No 1234/2008 has started on 20 August 2012. As the reference and concerned Member States were not able to reach an agreement in respect of the variation, on 30 October 2012, the United Kingdom initiated a referral procedure under Article 13(2) of Commission Regulation (EC) No 1234/2008.

## 2. Assessment of the data submitted

In order to address the concerns raised by the Netherlands, the MAH was requested to provide all available residue data for use of the product in chickens at the dose of 20 mg/kg body weight, together with an expert comment on the data and a justification for the meat withdrawal period in chickens. The current CVMP guidance on the establishment of withdrawal periods had to be taken into account.

**Residue depletion studies**

The MAH has provided data from three residue depletion studies.

Residue depletion data from a study conducted in 1993 have been provided. The correct number of animals was used and all of the other study details were in accordance with current requirements. Based on the results of the study a chicken meat withdrawal period of 5 days was supported using the CVMP accepted alternative approach. The main shortcoming of the study was the use of a microbiological assay. When microbiological methods of analysis are used, the data they generate can

be used in support of a proposal, depending on how well the method had been validated. Moreover, these older studies are superseded if data derived using more up to date and more accurate analytical methods based on chromatography and mass spectroscopy are available. Furthermore, the test product and Soludox 500 mg/g powder for use in drinking water for pigs and chickens have different composition.

Residue depletion data from a study conducted in 1999 have been provided. The correct number of animals was used and all of the other study details were in accordance with current requirements. The animals were given the correct dose and the product was administered appropriately. Based on the results a chicken meat withdrawal period of 12 days was supported using the CVMP accepted statistical approach.

Residue depletion data from a study conducted in 2011 have been provided. The study was well conducted and reported. The animals were given the correct dose and the product was administered appropriately and sufficient numbers of animals were used. Doxycycline residue levels in muscle were below the muscle MRL from 5 days onwards. Residue levels in the other tissues were below their respective MRLs from 4 days onwards. Based on the results from this study which was assessed during the variation application and was deemed adequately performed a chicken meat withdrawal period of 6 days was supported using the CVMP accepted alternative approach.

**Determination of the withdrawal period for chicken for the dose of 20 mg/kg body weight for 4 consecutive days**

A well conducted residue depletion study using the actual product at the maximum dose for the maximum duration of treatment is considered the most appropriate way to generate data to determine a suitable withdrawal period for a product. In this particular case, two residue studies from 1999 and 2011 using the actual formulation at the recommended dose were available. The CVMP has considered whether the differences in the conduct between the two latter residue depletion studies could be used to explain the disparity seen in the resulting withdrawal periods. The only significant differences between the conduct of the two studies was with the age and weight of the birds used. However, it is not felt that this can be used to support the MAH's disregard for the 1999 study since birds of various weights and from different breeds will be treated with this product. In particular, there is no reason to disregard this study considering that, within the European Union, chickens used for food production may differ considerably by breed, size and age. In fact, by using a range of chickens with different ages and weights would allow for both faster and slower growing broiler breeds to be included in the derivation of the meat withdrawal period.

The MAH has claimed that the findings from the 2011 study were in line with all other studies with similar and bioequivalent products conducted in Europe in recent years. As a result, the MAH proposes a meat withdrawal period of 6 days in chickens for Soludox 500 mg/g powder for use in drinking water for pigs and chickens when medicated at a dose of 20 mg/kg for 4 consecutive days. In support of this, an argument has been provided regarding the aligning of the withdrawal period for the product under discussion with those for other similar products on the grounds that bioequivalence can be assumed since it is an oral solution and the active substance is fully solubilised when in aqueous solution. However, due to the legal basis of the variation application under consideration, the MAH had provided their own residue depletion data to support a withdrawal period and only these data must be considered.

Following the review of all the data provided, the CVMP considered that only the two later residues depletion studies (from 1999 and 2011) should be taken into account in order to establish a withdrawal period for chicken meat and offal at a dose rate of 20 mg/kg body weight for 4 consecutive days.

Two options for deriving an overall withdrawal period were therefore considered:

Option (1) - evaluate each study independently and choose the longer withdrawal period as the overall withdrawal period for the product, as this would represent the worst-case scenario. Since in the 2011 study, the statistical method could not be used, a withdrawal period of 6 days could be calculated, using the alternative approach. The data from the 1999 study could be analysed using the statistical approach, leading to a withdrawal period of 12 days. This approach would then result in an overall withdrawal period of 12 days.

Option (2) - combine the data from the two studies as, provided that the studies are of acceptable quality, two experiments could result in a better estimate of the 'true' withdrawal period.

The combined muscle data using the actual values including those below the limit of quantification, a statistically derived meat withdrawal period of 9 days is obtained (F-test: <0.025; Cochran: >0.05; Bartlett: >0.05; Shapiro: >0.10). It was not possible to calculate the meat withdrawal period using the alternative approach as one sample contained residue levels at the MRL level at the last time point (8 days).

The Committee considered that the second approach was the most appropriate in this case.

# 3. Benefit-risk assessment

The CVMP considers that the MAH has not provided a sound justification as to why the findings from the 1999 residue depletion study should be ignored. The only significant differences between the conduct of the 1999 and 2011 studies were with the age and weight of the birds used. It is not felt that this can be used to support the MAH's disregard for the 1999 study since birds of various breed, weight and age will be treated with this product. In fact, by using a range of chickens with different ages and weights would allow for both faster and slower growing broiler breeds to be included in the derivation of the meat withdrawal period. Therefore, it is concluded that data from all available studies should be considered relevant, and as such, must be taken into account. As a result, the withdrawal period of 6 days, as proposed by the MAH, is considered to be inadequate to ensure consumer safety. Instead, a 9 days withdrawal period for chicken meat and offal is recommended following a dose rate of 20 mg/kg body weight for 4 consecutive days. This withdrawal period takes into account all the available data and is determined using the statistical approach. This revised withdrawal period of 9 days is considered appropriate to ensure the safety of the consumer.

# 4. Re-examination procedure

Following the CVMP opinion of 7 March 2013 recommending a 9 days withdrawal period for chicken meat and offal following a dose rate of 20 mg/kg body weight for 4 consecutive days, on 22 March 2013, Eurovet Animal Health BV notified the Agency of their intention to request a re-examination of the CVMP opinion. The detailed grounds for re-examination were submitted on 26 April 2013.

The MAH's grounds for re-examination focused on the fact that, as a powder for oral administration via the drinking water, Soludox can be considered to be bioequivalent to all other doxyclycline containing products for use in drinking water, and that therefore, the shorter withdrawal periods approved for these products would also be appropriate for Soludox. The MAH argued that even though Soludox contains tartaric acid as a stabiliser while all other doxycycline powders contain citric acid, the solubility of all products is the same and hence the amount of active substance in the chicken's tissues would be the same. In the opinion of the MAH the pH of the medicated drinking water solutions is mainly dependant on the quality of the water used, while the formulation of the powder, i.e. which acid is used as a stabiliser, has only a limited effect.

Regarding the residue depletion studies that were submitted, the MAH could not explain why the studies lead to different withdrawal periods. One possibility which could partially explain this difference was argued to be the fact that in the 1999 study, the litter was not removed, leading to a recirculation of doxycycline through the natural pecking behaviour of the chickens. The end result of that study was a withdrawal period of 12 days, whereas the 2011 study and all other studies for products that the MAH considered bioequivalent lead to a shorter withdrawal period. Therefore, the MAH concluded that the 1999 study should be disregarded and only the results of the 2011 study should be taken into account in establishing a withdrawal period, as these also correspond with the conclusions drawn in relation to other marketed products.

**CVMP conclusions after the re-examination**

The CVMP assessed the detailed grounds for re-examination presented by Eurovet Animal Health BV related to formulation effects and bioequivalence claims, and also to the available residue depletion studies.

The CVMP agreed that there is likely to be no significant difference in the solubility of the products on the market regardless of whether they contain tartaric acid or citric acid. However, the apparent similarity of solubility within drinking water should not be understood as providing an argument for ruling out definitively a formulation effect due to the presence of tartaric acid. Because of the presence of tartaric acid in this formulation, the results from the two residue studies are considered valid for assessment, pivotal and necessary in establishing a withdrawal period.

As to the comparison to other powders for use in drinking water containing doxycycline it is not possible to extrapolate the kinetics of doxycycline from the powders for use in drinking water containing doxycycline and citric acid to Soludox. In this case, where comparison is made between a product containing tartaric acid and another containing citric acid, and a formulation effect cannot be excluded due to the unknown impact of tartaric acid in the intestine, bioequivalence would have to be established through *in vivo* studies.

Since the arguments presented in relation to lack of formulation effect and bioequivalence are not considered to be conclusive, the withdrawal period must be based on the assessment of the residue depletion studies.

Two residue depletion studies, one from 1999 and one from 2011, were considered by the CVMP as providing adequate data from which to derive a withdrawal period. The MAH could not provide a sound scientific justification for dismissing the results from the 1999 study and considering only the most recent study.

After reviewing the documentation submitted by the MAH, the CVMP concluded that there were not sufficient scientific grounds to revise its conclusions of 7 March 2013, which recommended a withdrawal period of 9 days for chicken for the dose of 20 mg/kg bw for 4 consecutive days.

# Grounds for the variation to the terms of the marketing authorisations

Whereas

- the CVMP reviewed all available data submitted by the MAH, to support the withdrawal period for chicken meat and offal at a dose rate of 20 mg/kg body weight for 4 consecutive days;
- the CVMP on the basis of the available residue depletion data considered that a withdrawal period of 9 days should be established for chicken meat and offal at a dose rate of 20 mg/kg body weight for 4 consecutive days;

the CVMP recommended the granting of the variation to the terms of the marketing authorisations for Soludox 500 mg/g powder for use in drinking water for pigs and chickens (NL/V/0141/001/DC) and Soludox 500 mg/g powder for use in drinking water for pigs and chickens (UK/V/0349/001/DC) in accordance with the recommended changes in the relevant sections of the product information as set out in Annex III.

# Annex III

# Amendments in the relevant sections of the summary of product characteristics, labelling and package leaflet

# Summary of Product Characteristics:

**4.11 Withdrawal period(s)**

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Chickens:

……..

- Meat and offal: 9 days, following a dose rate of 20 mg/kg body weight for 4 days.

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# Labelling:

**8. WITHDRAWAL PERIOD**

……..

Chickens:

……..

- Meat and offal: 9 days, following a dose rate of 20 mg/kg body weight for 4 days.

……..

# Package leaflet:

**10. WITHDRAWAL PERIOD**

……..

Chickens:

……..

- Meat and offal: 9 days, following a dose rate of 20 mg/kg body weight for 4 days.

……..