Annex I

List of the names, pharmaceutical form, strength of the veterinary medicinal product, animal species, route of administration, applicant in the Member States

Member State EU / EEA	Applicant	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
Belgium	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
Czech Republic	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
Denmark	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
France	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
Germany	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral

Member State EU/EEA	Applicant	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Greece	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
Hungary	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
Ireland	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
Italy	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
Luxembourg	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
Poland	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral

Member State EU / EEA	Applicant	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Portugal	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
Slovakia	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
Spain	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
The Netherlands	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral
United Kingdom	Eurovet Animal Health BV Handelsweg 25 NL-5531 AE Bladel The Netherlands	Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys	Amoxicillin trihydrate	800 mg/g	Powder for use in drinking water	Chickens (broilers, pullets, breeders), ducks (broilers, breeders), turkeys	Oral

Annex II

Scientific conclusions and grounds for the granting of the marketing authorisations and amendment of the summary of product characteristics and package leaflet

Overall summary of the scientific evaluation of Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys (see Annex I)

1. Introduction

Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys (thereafter called 'Solamocta') contains 800 mg amoxicillin trihydrate (equivalent to 697 mg amoxicillin) as an active substance per gram product. Amoxicillin is a bactericidal antibiotic belonging to the semisynthetic penicillin group. Solamocta is indicated for treatment of infections in chickens, turkeys and ducks caused by bacteria susceptible to amoxicillin. The recommended dosage for chickens is 13.1 mg amoxicillin (equivalent to 18.8 mg veterinary medicinal product) per kg body weight for 3 days or in severe cases for 5 days. For ducks the recommended dosage is 17.4 mg amoxicillin (equivalent to 25 mg veterinary medicinal product) per kg body weight for 3 consecutive days. For turkeys the recommended dosage is 13.1-17.4 mg amoxicillin (equivalent to 18.8 to 25 mg veterinary medicinal product) per kg body weight for 3 days or in severe cases for 5 days.

The applicant Eurovet Animal Health B.V. submitted a marketing authorisation application, via the decentralised procedure, for Solamocta according to Article 13(3) of Directive 2001/82/EC, referring to the reference product Amoxinsol 100% w/w Powder for Oral Solution authorised in the United Kingdom. The marketing authorisation application was submitted to the United Kingdom as reference Member State and Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Poland, Portugal, Slovakia, Spain and The Netherlands as concerned Member States.

During the decentralised procedure Denmark, as a concerned Member State, considered that Solamocta may present a potential serious risk to human and animal health. In particular, Denmark considered that Solamocta is essentially different from the reference product Amoxinsol and that these differences could be sufficient to require a formal bioequivalence study. In addition, Denmark raised a concern that the advice for prudent use in the product information is insufficient, particularly in the context of increasing concerns regarding development of antimicrobial resistance and the widespread use of in-feed and in-water antimicrobial products. These issues remained unresolved and therefore a referral under Article 33(1) of Directive 2001/82/EC to the Coordination group for Mutual recognition and Decentralised procedures (veterinary) (CMD(v)) was started. Since the issues raised by Denmark remained unresolved, the Member States concerned failed to reach agreement regarding the marketing authorisation for the product Solamocta and consequently the matter was referred to the CVMP on 28 May 2015 under Article 33(4) of Directive 2001/82/EC.

The CVMP was asked to consider the issues raised by Denmark and conclude whether marketing authorisations for Solamocta should be granted.

2. Assessment of the data submitted

In this procedure, the CVMP was asked to consider whether the available data related to Solamocta is sufficient to support exemption from the requirement for bioequivalence studies in accordance with section 7.1.c) of the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2)[1]. In addition, the CVMP was asked to consider if the proposed

[1] CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/04/WC500105372.pdf

advice for prudent use in the product information is appropriate and provide the end-user with sufficient advice for the prudent use of this antimicrobial product.

Exemption from the requirement for bioequivalence studies

The applicant has claimed exemption from the requirement for bioequivalence studies in accordance with section 7.1.c) of the aforementioned CVMP guideline (EMA/CVMP/016/00-Rev.2).

The composition of Solamocta differs to that of the reference product (Amoxinsol 100% w/w Powder for Oral Solution) in that it contains only 80% w/w amoxicillin trihydrate and in addition three excipients (sodium carbonate monohydrate, sodium citrate and colloidal anhydrous silica) that are not present in the reference product. However, both products are aqueous oral solutions at the time of administration, containing an identical concentration of amoxicillin.

The rationale for the inclusion of the excipients was provided. Sodium carbonate increases the pH of the solution allowing more concentrated solutions to be used and therefore facilitating administration via automatic water supply systems. Sodium citrate binds calcium and magnesium ions (present in hard water) and prevents the formation of insoluble carbonate salts. Colloidal anhydrous silica is a flow aid.

Each of these excipients is well-established and widely used in medicinal products and foodstuffs. No reference can be found to any evidence that they can affect the gastrointestinal transit, absorption or *in vivo* stability of amoxicillin. The formulation of Solamocta does not alter the pH of the medicated drinking water beyond the naturally occurring range of drinking water.

It is therefore considered that the applicant has demonstrated compliance with the requirements of section 7.1.c) of the abovementioned CVMP guideline (EMA/CVMP/016/00-Rev.2), allowing bridging to the safety and efficacy data associated with the reference product.

Solubility

The applicant has provided all solubility data as required by the CVMP guideline on quality aspects of pharmaceutical veterinary medicines for administration via drinking water (EMEA/CVMP/540/03-Rev.1)[2].

They have demonstrated that the highest therapeutic concentration is fully soluble within 10 minutes in hard/high pH water and soft/low pH water and have determined the maximum solubility (within 10 minutes) in water of different qualities and different temperatures, including very cold (4 °C) water.

These data have been used to specify appropriate product administration instructions in the Summary of Product Characteristics (SPC) section 4.9 Amounts to be administered and administration route, which will ensure that Solamocta will be fully in solution at the time of administration at the appropriate therapeutic concentration.

Extrapolation of the safety and efficacy of the reference product to Solamocta

Given the legal basis of this application (under Article 13(3) of Directive 2001/82/EC – a hybrid or mixed application) and the satisfactory justification for a waiver from the requirement to demonstrate *in vivo* bioequivalence with the reference product in accordance with section 7.1.c) of the abovementioned CVMP guideline (EMA/CVMP/016/00-Rev.2), it is considered that the safety and efficacy of amoxicillin can be extrapolated from that of the reference product.

[2] CVMP guideline on quality aspects of pharmaceutical veterinary medicines for administration via drinking water EMEA/CVMP/540/03-Rev.1) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004462.pdf

Solamocta contains sodium carbonate monohydrate as a solubility improvement agent, sodium citrate as a complexing agent and silica colloidal anhydrous as a flow conditioning agent. These excipients have well-established use in other similar EU-authorised veterinary medicinal products and are of negligible toxicological concern at the proposed administration rate.

Advice for prudent use

Amendments to the SPC text have been proposed to address responsible use in relation to development of antimicrobial resistance in order to minimise the risk to both animal and public health.

The SPC section 4.5 Special precautions for use in animals, now includes the standard wording regarding use based on susceptibility testing where possible and advising to follow the instructions given in the product information, and the SPC section 5.1 Pharmacodynamic properties, now includes up-to-date information regarding the mode of action of amoxicillin and the three main mechanisms of resistance to beta-lactams. The warnings are in line with CVMP guideline on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005)[3].

3. Benefit-risk assessment

A satisfactory justification has been provided that the product, Solamocta, is eligible for a waiver from the requirement to demonstrate *in vivo* bioequivalence with the reference product in accordance with section 7.1.c) of the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) and that the excipients will not impact the bioavailability or safety of this product compared to the reference product. Sufficient guidance is provided in the product information to ensure that the product can be properly prepared and is fully in solution at the time of administration in accordance with the requirements for the therapeutic dose. Advice on prudent use has been proposed to address responsible use in relation to development of antimicrobial resistance.

Overall, the CVMP considered that the concerns expressed by Denmark should not prevent the granting of marketing authorisations and the benefit-risk evaluation is deemed to be positive for Solamocta provided that the product information is amended to include revised instructions on product administration and prudent use warnings.

Grounds for the granting of the marketing authorisations for Solamocta

Having considered all the data submitted the CVMP concluded that:

- The applicant has demonstrated compliance with the requirements of section 7.1.c) of the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2), and exemption from the requirement for bioequivalence studies.
- Revised information on solubility and advice on prudent use should be included in the product information.

Therefore, the CVMP recommended granting of the marketing authorisation for the veterinary medicinal products referred to in Annex I with amendments to the summary of product characteristics and package leaflet of the reference Member State. The amended sections of the summary of product characteristics and package leaflet of the reference Member State are set out in Annex III.

[3] CVMP guideline on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/02/WC500070670.pdf

Annex III

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

The valid summary of product characteristics, labelling and package leaflet are the final versions achieved during the Coordination Group procedure with the following amendments:

Add the following text in the relevant sections of the product information:

Summary of Product Characteristics

4.5 Special precautions for use

Special precautions for use in animals

Official, national and regional antimicrobial policies should be taken into account when the product is used. Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria. Use of the product deviating from the instructions given in the summary of product characteristics may increase the prevalence of bacterial resistance to amoxicillin and may decrease its effectiveness.

4.9 Amounts to be administered and administration route

In drinking water use. Prepare the solution with fresh tap water immediately before use. Any unused medicated water should be discarded after 12 hours. In order to ensure consumption of the medicated water, animals should not have access to other water supplies whilst being treated. The following formula may be used to calculate the required concentration of product (in milligrams of product per litre drinking water):

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

To ensure a correct dosage, body weight should be determined as accurately as possible to avoid underdosing. The uptake of medicated water depends on the clinical condition of the birds. In order to obtain the correct dosage the concentration of amoxicillin has to be adjusted taking into account water intake. After the end of the medication period the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of the active substance. Maximum solubility of the product in water of at least 10 °C is approximately 6 g/l within 10 minutes. At lower temperatures (4 °C), the maximum solubility is approximately 5 g/l within 10 minutes.

Chickens

The recommended dosage is 13.1 mg amoxicillin (equivalent to 18.8 mg veterinary medicinal product) per kg body weight for 3 days or in severe cases for 5 days.

Ducks

Recommended dosage is 17.4 mg amoxicillin (equivalent to 25 mg veterinary medicinal product) per kg body weight for 3 consecutive days.

Turkeys

Recommended dosage is 13.1-17.4 mg amoxicillin (equivalent to 18.8 to 25 mg veterinary medicinal product) per kg body weight for 3 days or in severe cases for 5 days.

5.1 Pharmacodynamic properties

Amoxicillin is a time-dependent bactericidal antibiotic which acts by inhibiting the synthesis of bacterial cell walls during bacterial replication. It inhibits the formation of bridges between the chains of linear polymers constituting the peptidoglycan cell wall of Gram positive bacteria.

Amoxicillin is a broad-spectrum penicillin. It is also active against a limited range of Gram negative bacteria on which the outer layer of the bacterial cell wall is composed of lipopolysaccharide and proteins.

There are three main mechanisms of resistance to beta-lactams: beta-lactamase production, altered expression and/or modification of penicillin binding proteins (PBP), and decreased penetration of the outer membrane. One of the most important is the inactivation of penicillin by beta-lactamase enzymes produced by certain bacteria. These enzymes are capable of cleaving the beta-lactam ring of penicillins, making them inactive. The beta-lactamase could be encoded in chromosomal or plasmidic genes.

Cross-resistance is observed between amoxicillin and other penicillins, particularly with aminopenicillins.

The use of extended spectrum beta-lactam drugs (e.g. aminopenicillins) might lead to the selection of multi-resistant bacterial phenotypes (e.g. those producing extended spectrum beta-lactamases (ESBLs)).

Package leaflet

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

In drinking water use. Prepare the solution with fresh tap water immediately before use. Any unused medicated water should be discarded after 12 hours. In order to ensure consumption of the medicated water, animals should not have access to other water supplies whilst being treated. The following formula may be used to calculate the required concentration of product (in milligrams of product per litre drinking water):

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

To ensure a correct dosage, body weight should be determined as accurately as possible to avoid underdosing. The uptake of medicated water depends on the clinical condition of the birds. In order to obtain the correct dosage the concentration of amoxicillin has to be adjusted taking into account water intake. After the end of the medication period the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of the active substance. Maximum solubility of the product in water of at least 10 °C is approximately 6 g/l within 10 minutes. At lower temperatures (4 °C), the maximum solubility is approximately 5 g/l within 10 minutes.

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Recommended dosage is 17.4 mg amoxicillin (equivalent to 25 mg veterinary medicinal product) per kg body weight for 3 consecutive days.

Turkeys

Recommended dosage is 13.1–17.4 mg amoxicillin (equivalent to 18.8 to 25 mg veterinary medicinal product) per kg body weight for 3 days or in severe cases for 5 days.

12. SPECIAL WARNINGS

Special precautions for use in animals:

Official, national and regional antimicrobial policies should be taken into account when the product is used. Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria. Use of the product deviating from the instructions given in the summary of product characteristics may increase the prevalence of bacterial resistance to amoxicillin and may decrease its effectiveness.