Divergent position on a CVMP opinion on an Article 33(4) referral of Directive 2001/82/EC for

Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys (EMEA/V/A/112)

We, the undersigned, have a divergent position on the marketing authorisation of Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys.

Eurovet Animal Health B.V. submitted an application for a decentralised procedure, under Article 13(3) of Directive 2001/82/EC – generic hybrid application for Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys (formerly Octapoultry 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys) on 25 March 2014.

Denmark raised objections that the product Solamocta is essentially different from the reference product Amoxinsol 100% w/w Powder for Oral Solution and that these differences could be sufficient to require a formal bioequivalence study.

The areas of specific concern include the following:

- The different strength of Solamocta compared to the reference product Amoxinsol.
- The presence of excipients in Solamocta which are not present in the reference product, specifically sodium carbonate, which increase the dissolution rate and solubility of the active substance.
- The conduct of solubility tests to determine maximum solubility at 10°C, rather than 4°C.

There are major concerns about the legal basis chosen by the applicant and previous RMS for using Article 13(3). The reference product used in this procedure was Amoxinsol 100% w/w Powder for Oral Solution. The two products are essentially different in several respects, including:

	Solamocta	**Amoxinsol**
Active substance	**Amoxicillin trihydrate**	**Amoxicillin trihydrate**
Strength	**800 mg/g**	**1000 mg/g**
Excipients	**Sodium carbonate monohydrate** **Sodium citrate** **Silica colloidal anhydrous**	**None**

Doses	**Chickens: 13.1 mg/kg** **Ducks: 17.4 mg/kg** **Turkeys: 13.1-17.4 mg/kg**	**Chickens: 15 mg/kg** **Ducks: 20 mg/kg** **Turkeys: 15-20 mg/kg**

The dose appears different between Solamocta and the reference product, Amoxinsol 100% w/w Powder for Oral Solution, due to the fact that the applicant for Solamocta insists on stating the dose in terms of amoxicillin and not amoxicillin trihydrate. The reference product as well as all other similar products on the European market state the dose in terms of amoxicillin trihydrate.

The generic, Solamocta, has excipients, particularly sodium carbonate, which is well known to raise the pH of the drinking water, in particular soft water, and thereby increases the solubility and dissolution rate of the active substance (amoxicillin). The solubility of amoxicillin trihydrate is limited by pH. Solubility is higher at higher pHs, therefore the addition of buffers increases the maximum solubility in drinking water, above that from the reference product with no excipients.

There are other products available on the European market that are identical to Solamocta in terms of having the identical active substance and strength, with either identical excipients or very similar. Thus, an Article 13(1) procedure could have been chosen in this case, with a more appropriate reference product, and it is unclear as to why an Article 13(3) was chosen.

According to Directive 2001/82/EC, as amended by Directive 2004/28/EC the definition of a generic product includes:

"generic medicinal product" shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies …

As such, Solamocta does not fulfil the strict definition of a generic product to the reference product, Amoxinsol 100% w/w Powder for Oral Solution. According to the CMD(v)/GUI/014 (GUIDANCE for The Processing of Generic Applications Through MRP/DCP), it states the following for Article 13(3) Hybrid applications:

The results of appropriate tests and trials shall be provided in cases where the application does not:

i. fall under the strict definition of a generic product, or

ii. where it is not possible to demonstrate bio-equivalence to the reference product, or

iii. where there are changes to the active substance, therapeutic indications, strength, pharmaceutical form or route of administration from the reference product.

In practical terms this means that the applicant can cite a reference product but needs to provide bridging data to account for the differences between the proposed product and the reference product …

This implies that the applicant was required to provide appropriate tests and trials since Solamocta does not "i. fall under the strict definition of a generic product", and "iii. there are changes to the … strength, pharmaceutical form … from the reference product".

However, at the same time the applicant requested a biowaiver from bioequivalence that was accepted by the RMS despite the major differences between the generic and reference. Thus, no appropriate tests and trials were performed. Instead, what was provided as "bridging data" is some

fragmented *in vitro* studies of stock solutions comparing the maximum solubility between the two products at different water temperatures.

Beginning at 10°C, there is a marked difference between the reference and generic products in the percentage (%) of amoxicillin in solution after stirring for 10 minutes, at maximum solubility. This difference is more marked at 4°C, as well as the fact that the generic product (Solamocta) is below the in-use product specification of 90-105% at 4°C. Thus, there are doubts as to the similarity of the concentration of the active substance, in an aqueous oral solution, between the reference and generic products based on water temperature, at the time of administration. This difference in the solubility of amoxicillin trihydrate is recognised in some of the SPCs of products for drinking water. At all water temperatures tested there was no similarity in the maximum solubility between the reference and generic products.

In this CVMP Article 33(4) referral the applicant has provided new data on a study conducted whereby both Solamocta and the reference product, Amoxinsol, were mixed in water (hard and soft water), both at 4°C and 10°C, at 'therapeutic' concentrations for the active substance, according to the SPC.

Although, this data appears to be in the favour of the applicant, there are major concerns about this study, and does NOT contain enough information to form an opinion on the validity of the study, including:

- No GLP certificate provided for this new study.
- No specifications of the study description provided:
    - No mention if the study was repeated three times, as per the normal standards.
    - No mention as to how the products were mixed.
    - No measurements of pH in the final solution.
    - No mention as to the volume of water used to mix the products.
    - No mention as to the methods used for the amoxicillin assay.
    - No data provided concerning the accuracy of the analytical methods.

Furthermore, it is difficult to define the meaning of a 'therapeutic' concentration for different poultry species. For example, many different medicine administration systems are currently in use in the poultry industry, including smaller mixing tanks that feed directly into the drinking water supply. For these systems, more concentrated solutions will obviously be made, close to maximum solubility, compared to adding amoxicillin trihydrate direct to a large drinking water tank (e.g. header tank).

The applicant used a 'therapeutic' concentration of 300 mg/Litre for the Solamocta but it is unclear as to the basis for this choice of therapeutic concentration. The calculations that derived this therapeutic concentration were not explained by the applicant. When attempting to repeat these calculations, higher 'therapeutic' concentrations were identified for heavier bird species (e.g. ducks and turkeys) that are included in the SPC. Also, the formula stated on the SPC that is used to calculate the 'therapeutic' concentration is partly based on average daily water consumption. Water requirements are very difficult to determine in poultry species and average daily water consumption can be misleading, due to the many factors that influence water intake of birds, including:

a) Environmental temperature,

b) Relative humidity,

c) Composition of the diet,

d) Type of production

e) Individual variation of kidney water resorption.

In the case of the reference product, 750 mg/litre amoxicillin trihydrate was used for the residue depletion study.

We, the undersigned, have a divergent position on the marketing authorisation of Solamocta 697 mg/g Powder for Use in Drinking Water for Chickens, Ducks and Turkeys, in that it is not bioequivalent to the reference product, Amoxinsol 100% w/w Powder for Oral Solution, due to:

- Marked differences in maximum solubility based on water temperature between the reference and generic products. This will lead to differences in the concentration of the active substance in an aqueous oral solution, based on water temperature, and thus does not qualify for a biowaiver exemption from bioequivalence studies.
- Differences in the strength of the formulation in this generic product compared to the reference product.
- Addition of excipients in this generic product compared to the reference. Specifically, the generic has an excipient added as sodium carbonate which raises the pH of the drinking water, in particular soft water, and thereby increases the solubility and dissolution rate of the active substance (amoxicillin). The solubility of amoxicillin trihydrate is limited by pH. Solubility is higher at higher pHs, therefore addition of buffers increases the maximum solubility that can be achieved. The reference product does not have this excipient.
- A new study on solubility at ‘therapeutic’ drinking water concentrations is poorly described and without the necessary information to perform an assessment.

Oral bioavailability is very likely higher with the generic product, Solamocta because of the new excipient, sodium carbonate, and higher solubility at different water temperatures. Hence, safety and efficacy, including withdrawal time studies of the new product should have been based on original studies, since these two products are not bioequivalent.

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