College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Oxuvar 5.7%, 41 mg/ml concentrate for solution for honey bees

Created: December 2019

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0214/001/MR
Name, strength and pharmaceutical form	Oxuvar 5.7%, 41 mg/ml concentrate for solution for honey bees
Applicant	Andermatt BioVet GmbH Franz-Ehret-Str. 18 79541 Lörrach Germany
Active substance(s)	Oxalic acid 41.0 mg (equal to 57.4 mg oxalic acid dihydrate)
ATC Vetcode	QP53AG03
Target species	Honey bee (*Apis mellifera*)
Indication for use	Treatment of varroosis on honey bees (*Apis mellifera*) due to varroa mites (*Varroa destructor*).

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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Well established use application in accordance with Article 13.1(a) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	21 September 2016
Date product first authorised in the Reference Member State (MRP only)	13 February 2016
Concerned Member States for original procedure	AT, BE, CZ, DE, HR, HU, IT, PT, SI, SK, UK

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.

The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.

The efficacy of the product was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains oxalic acid 5.7% in water.

The product is a clear colourless solution in bottles of 0.5 and 2L. The solution should be mixed before use with sugar for the trickling application or with drinking water for the spraying application.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

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B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is oxalic acid, an established substance described in the German Homeopathic Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

D. Control on intermediate products

The content of oxalic acid dihydrate in the OXUVAR 5.7% (m/V) bulk is tested in house by titration.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. Stability

The active substance is fully tested prior to the first use in manufacture of the product. Thereafter, a re-test period of 3 years is justified.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

With regards to the ready-to-use spraying solution the applicant started a 60 month in-use stability study according to the valid test program provided. A preliminary one year in-use stability shelf-life has already been accepted. After finalising the in-use stability test program a 5 year in-use shelf life is foreseen.

A commitment has been provided that out of specification data or potentially out of specification data at the end of the proposed in-use shelf life will be provided immediately to the competent authorities (with proposed action).

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G. Other Information

Oxalic acid in aqueous solution remains stable. Yet, in the presence of sugar in the solution the oxalic acid strongly promotes the degradation of the sugar. Some of the sugar degradation products are toxic to bees, for example hydroxymethylfurfural (HMF).

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that oxalic acid is an end-product of metabolism of natural components in mammals. In humans, endogenous sources constitute approximately 30-70% of the oxalic acid excreted daily via urine. The fecal excretion mainly results from dietary oxalic acid intake.

After oral administration via gavage or diet, the absorption was limited in rodent (less than 30%) and humans (3-20%). The degree of absorption was largely dependent on factors such as pH conditions in the intestinal tract, on the presence of free ionized calcium ions and other cations and on the presence of oxalate-degrading bacteria in the human gut. Highest concentrations of oxalic acid are found in kidneys.

Oxuvar 5.7% contains oxalic acid, which is a strong acid. Its mode of action is not clear, but may be attributed to the acid pH.

Toxicological Studies

The applicant has provided bibliographical data which show that

- Single Dose Toxicity

Oxalic acid is acute toxic after oral ingestion, with kidney as the main target organ. Oxalic acid can cause neurotoxicity and cardiac arrest. Oral LD_{50} values were determined to be 375-475 mg/kg in a rat study; 1 g in a dog study and 200 mg in a cat study. In humans, fatalities have been observed after doses of 3 grams or more per person.

Acute dermal toxicity is described to be low; no toxic levels have been described, though topical levels of 20000 mg/kg did not result in deaths in a rabbit study.

- Repeated Dose Toxicity

Nephrotoxicity was found in rats following the subcutaneous administration of oxalic acid during 5 days a week for 2 weeks at doses ≥ 25 mg/kg bw. Studies provided on repeated dose toxicity exhibited several deficiencies with regard to current guidelines. It was not possible to retain a NOEL following repeated dose oral administration of oxalic acid to rats.

- Reproductive Toxicity, including Teratogenicity

Oxalic acid caused embryotoxicity in mice at a dose of 275 mg/kg bw (0.2% in drinking water; effects on prostate weight, number of pups/litters, live pup weight and for effects on kidney and sperm production in F1 generation). No NOEL was derived.

- Mutagenicity/Carcinogenicity

Based on the outcomes of an Ames test, chromosome aberration test and carcinogenicity study it was concluded that oxalic acid does not have mutagenic or carcinogenic properties.

Other Studies

The applicant has provided limited information on irritating properties of oxalic acid and concluded that oxalic acid causes skin irritation and/or serious eye irritation. This is in line with the strong acidic properties of oxalic acid and with the notified classifications given by ECHA; H314 (Causes severe skin burns and eye damage), H315 (Causes skin irritation), H318 (Causes serious eye damage) and H319 (causes serious eye irritation). Due to its corrosive properties, irritation can be expected after inhalation. Oxalic acid is not considered a skin sensitizer.

Observations in Humans

In humans, fatalities have been observed after doses of 3 grams or more per person.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that:

Oral exposure
Current product is very acidic (pH 0.5-1.5). Therefore, the ingestion of small amounts (droplets) may result in severe adverse effects. Oral exposure due to hand-to-mouth contact is not expected as the user will wear gloves. The packaging has demonstrated to be child-resistant.

Dermal exposure
Serious local effects are expected after dermal contact because of its corrosive properties. This requests the wearing of personal protective equipment including chemical-resistant gloves. This will significantly mitigate exposure and reduce local (as well as systemic) effects. Moreover, based on a quantitative risk characterization it was concluded that the user will not be exposed in such a way that embryotoxic or reprotoxic effects will occur after dermal exposure.

Ocular exposure
Ocular exposure is estimated to be low. Exposure is not considered to play a significant role in systemic toxicity, though based on the corrosive properties of this product to result in local effects. Therefore, exposure of the eyes should be prevented by wearing safety glasses.

Exposure by inhalation
Inhalation of aerosols can be expected during spraying. As the product is acidic and irritating, small amounts could already lead to adverse effects on the respiratory system. Therefore, inhalation should be prevented by using respiratory protection. Moreover, based on a quantitative risk characterization it was concluded that the user will not be exposed in such a way that embryotoxic or reprotoxic effects will occur after exposure by inhalation. The user is the bee-keeper, which is considered to be a semi-professional. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

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Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:
The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment.
The veterinary medicinal product will only be used in non-food animals.

III.B Residues documentation

Residue Studies

The applicant has provided bibliographical data which describe that:

- Oxalic acid is a substance of endogenous origin which occurs in all mammalian species and in plants,
- Plant derived food constitutes the major source of dietary oxalic acid (estimated to be in the range of 5 to 500 mg/day), occasionally exceeding 1000 mg/day,
- Oxalic acid is occurring naturally in honey with a range of 1 to 800 mg/kg* and no significant increase of the natural content was observed following treatment of bees (in autumn or winter),
- The theoretical intake of oxalic acid in honey from either treated or non-treated hives is insignificant compared to the overall intake of oxalic acid in daily food from other sources.

*the intake of oxalic acid that would be expected in 20 g honey is in the range of 0.02 to16 mg/day.

Broodless swarms, artificial swarms and man-made broodless colonies can also be treated during summer (April-July). Also for this application - despite that these treated frames should not be used for honey production in the same season as indicated in the product information - it was calculated, assuming all oxalic acid would deposit in honey, that it would not result in a significant increase of oxalic acid in honey and be within the range of 1-800 mg/kg honey.

MRLs

Oxalic acid is listed in Table 1 of the MRL Regulation 37/2010

MRLs are listed below:

Marker residue	Animal Species	MRL (µg/kg)	Target Tissues
Not applicable	Bees	No MRL required	Not applicable

The MRL status of the excipients of the product Oxuvar 5.7% is indicated in the following table:

Excipient	MRL status
Decalcified drinking water	Out of Scope list

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Withdrawal Periods

Based on the data provided above, a withdrawal period of 0 days for honey is justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data to show that:

- Oxalic acid dihydrate probably acts on Varroa mites by contact due to the low pH.
- The addition of sucrose makes the solution more hygroscopic and at a relative humidity > 69% mortality of mites will increase.
- After trickling oxalic acid is spread from bee to bee by physical contact.
- Oxalic acid can penetrate the keratin layer after topical administration, although bees are likely to ingest some oxalic acid as well.

Tolerance in the Target Species of Animals

Oxalic acid has a slow toxic effect on bees (death rate is higher after 72 hours compared to 24 hours). LD50 at 72h was estimated to be 195-500µg/bee. Tissue distribution of oxalic acid in bee organs suggests that some of the acid is ingested by the bee. Ingestion of oxalic acid causes permanent lesions in digestive and excretory organs of the honey bee (up to 72 hours).

Several studies (Higes, Charriere 2004, Nanetti 2003) have compared winter treatment trickling oxalic dihydrate acid (3%-3.5%) in sugar (1:1) water with control colonies that did not receive winter treatment. Especially in Northern countries (The Netherlands) treatment did have a more negative effect on colony strength or colony losses in the following spring compared to untreated control colonies, which were also infested with *Varroa destructor*. This would mean that the threshold of the amount of Varroa mites in the tested control colonies is low and in these studies the risk/benefit analysis of winter treatment using oxalic acid could be considered negative when looking at clinical signs.

It has been demonstrated that repeated treatments with oxalic acid is more toxic to bees than a single treatment, especially in Northern countries. Bee larvae are more susceptible to the toxic effect of oxalic acid.

IV.B Clinical Studies

Several studies are included in the dossier. Conclusions from these studies are:

- Testing different combinations of oxalic acid (0, 2.1, 3.2 and 4.2%) with sucrose (0, 30, 60 and 70%) in various European countries, indicated optimal efficacy of 90.3-97.8% using oxalic acetate concentrations of 3.2% and 4.2% and showed sucrose is necessary for efficacy (30-60%). A 3.2% oxalic acetate solution is repeatedly demonstrated to be an acceptable alternative to 4.2%, but not when the dose was split in two administrations. 60% sucrose is slightly more effective than 30%, whereas solutions without sugar were not effective. Generally, winter survival in treated honey bees was similar to untreated controls.
- Efficacy increases with concentration of oxalic acid. Solutions of 3% oxalic acid or lower are considered suboptimal. 3.7% oxalic acid seems optimal, as 4.5% concentration was less tolerated.

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- Repeated treatment seems more toxic to honey bees than single treatment.
- Administering larger volumes per comb may lead to higher effectiveness but lower tolerance as well.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Summary of change	**Section updated**	**Approval date**
Change in the address of the marketing authorisation holder and change in the address of the manufacturing authorisation holder responsible for batch release (NL/V/xxxx/IA/035/G)	Module 1	4 June 2019