Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Varroxal 1 g/g Bee-hive Powder for Honey Bees

Date Created: March 2025

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Varroxal 1 g/g Bee-hive Powder for Honey Bees, Powder for bee-hive solution
Applicant	Andermatt BioVet GmbH, Franz-Ehret-Str. 18, 79541 Lorrach, 79541, Germany
Active substance	Oxalic Acid Dihydrate
ATC vet code	QP53AG03
Target species	Honey bees
Indication for use	Treatment of varroosis (*Varroa destructor*) of honey bees (*Apis mellifera*) in brood-free colonies.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full bibliographic application in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 7) as amended.
Date of conclusion of the procedure	04/02/25

I. SCIENTIFIC OVERVIEW

The product was submitted for a full bibliographic application in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 7) as amended.

Varroxal for Honey bees is a bee-hive powder containing 1 g/g oxalic acid dihydrate (equivalent to 0.71 g/g oxalic acid). The product can be administered via three routes of application: sublimination/evaporation, trickling, or spraying. for the treatment of varroosis (*Varroa destructor*) of honey bees (*Apis mellifera*) in brood-free colonies:

1. Evaporation/sublimination application: The product is administered to the broodless colony as a single treatment in autumn/winter at outdoor temperatures between 2°C and 10°C. A second evaporation treatment after a 2-week interval is only recommended for:
   - Heavily reinfested colonies (remaining infestation over 6%)
   - Colonies where patches of sealed brood cells are present during wintertime.

   The full contents of two spoonfuls of the product are placed into a suitable device for evaporation/sublimination to treat one colony.

2. Trickling application: The product is administered to the broodless colony in summer after the honey harvest or in autumn/winter as a single treatment at outdoor temperatures above -15°C.
   For treatment in northern and central Europe during winter, the full contents of eight spoonfuls of the product are mixed with 200 ml of lukewarm sugar syrup 1:1 (30 to 35°C) in a non-metallic container to obtain a 4% (m/V) oxalic acid dihydrate solution (which corresponds to a 2.8% (m/V) oxalic acid solution) to treat four colonies.
   For summer treatments in all of Europe, the full contents of twelve spoonfuls of the product are mixed with 200 ml lukewarm sugar syrup 1:1 in a non-metallic container to obtain a 6% (m/V) oxalic acid dihydrate solution (which corresponds to a 4.2% (m/V) oxalic acid solution) to treat four colonies.

Once fully dissolved, the solution is applied via syringe at a dose per comb of 0.25 ml/dm^2. For small frames, 3-4 ml solution is applied per row of brood frames and for large frames, 5-6 ml is applied per row of brood frames.

3. Spraying application: The product is administered to swarms, artificial swarms or man-made broodless colonies as a single treatment in spring/summer or in autumn/winter at outdoor temperatures above 8°C. A second spraying treatment after a 2-week interval is only recommended for heavily reinfested colonies with a remaining infestation of over 6%.The full contents of six spoonfuls of the product are mixed with 200 ml lukewarm tap water in a hand sprayer to obtain a 3% (m/V) oxalic acid dihydrate solution (which corresponds to a 2.1% (m/V) oxalic acid solution) to treat three colonies. Once dissolved, 2-4 ml of the solution is sprayed over each side of a comb covered by bees. If only half the comb is covered by bees, the dosage should be reduced by 50%. The maximum dose is 80 ml per hive. Man-made broodless colonies or swarms newly lodged in hives should be treated with a dose of 0.3 ml/dm^2 comb fully covered with bees. Swarms and artificial swarms in the cluster should be sprayed with 20-25 ml of the spraying solution per kg of bees.

The distribution category is AVM-GSL

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, any reactions observed are indicated in the SPC[1]. 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[2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains oxalic acid dihydrate with no excipients.

The container/closure system consists of 75 g and 200 g HDPE bottles closed with an ALU/HDPE seal and a HDPE/PP turn and lock cap, packed in a carboard box with a 1 g measuring spoon. The particulars of the containers and controls performed are provided and conform to the regulation.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

The choice of the formulation and the absence of preservative are justified.

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

II.B. Description of the Manufacturing Method

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

Process validation data on the product have been presented in accordance with the relevant regulatory guidelines.

II.C. Control of Starting Materials

The active substance is oxalic acid dihydrate, an established active substance described in the German Homeopathic Pharmacopeia (HAB). 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.

The product doesn't contain any excipients.

The standard packaging for oxalic acid dihydrate is a bag of 25 kg placed on pallets (up to 1250 kg per pallet). Bags consist of a double layer white PE film. The inner bag is white PE of 180 µm thickness, and the outer bag is white PE of 90 µm thickness.1250 kg units are wrapped with stretch foil for transportation and covered by an extra liner.

II.C.4. Substances of Biological Origin

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable

II.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 sites have been provided demonstrating compliance with the specification. Control tests on the finished product are those for:

- General characteristics of the finished product
- Identification and assay of the active substance

II.F. Stability

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

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

G. Other Information

The shelf life of the product as packaged for sale is 5 years. The instructions after first opening the immediate packaging are to use within the expiry date and the product should be used immediately after dissolution, according to directions.

The product should be stored in the original package in a dry place, protected from direct sunlight.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

In accordance with the application type, the applicant provided a substantial number of references from the published literature describing the pharmacology and toxicology of oxalic acid dihydrate.

III.A Safety Documentation

Pharmacological Studies

Bibliographical data has been provided which show that oxalic acid dihydrate acts as a contact poison for *Varroa destructor* mites attached to honey bees. The applicant has also provided bibliographical data which show that oxalic acid can penetrate the exoskeleton of honey bees. After administration of oxalic acid dihydrate by trickling, contamination of adult bees was detected at 24 hours, reaching a peak one day later. This declined rapidly following, reaching one sixtieth of the peak concentration at 11 days post-treatment. The presence of oxalic acid has been demonstrated in bee haemolymph and the gastrointestinal tract.

Toxicological Studies

The applicant has provided bibliographical data which address the acute and repeat-dose toxicity of oxalic acid in rats, mice, cats, dogs, rabbits, guinea pigs, sheep and horses.

- Single Dose Toxicity - Moderate to high toxicity following single-dose oral administration is evident for rats, cats and dogs. The oral LD_{50} (Median Lethal Dose) values determined for rats were 475 mg/kg bodyweight for males and 375 mg/kg bodyweight for females. For dogs and cats, the oral toxic doses were 1 g and 200 mg, respectively. After oral administration, the main effect is impairment of kidney function. After intravenous administration of about 40 mg/kg bodyweight to dogs, 100% of animals died shortly after administration due to neurotoxicity and cardiac arrest. The acute dermal toxicity LD_{50} of oxalic acid for rabbits is more than 20,000 mg/kg. At a dosage of 0.5 g/test animal no chemical burns were observed.
- Repeated Dose Toxicity - Reduced growth rate, renal toxicity and reduced thyroid gland function were observed in repeat-dose oral toxicity studies in rats, whereby a LOAEL (Lowest Observed Adverse Effect Level) of 1250 mg/kg is reported.
- Reproductive Toxicity, including Teratogenicity - Reproductive and developmental toxicity studies in mice, rats, and sheep conclude that oxalic is a weak reproductivity toxicant with embryotoxicity seen at a dose of approximately 2.75 mg/kg bodyweight per day. Oxalic acid has been found to cross the placental barrier in sheep but has not been found to induce teratogenic effects.
- Mutagenicity - Based on the studies provided oxalic acid is not considered mutagenetic or carcinogenic.

Observations in Humans

Oxalic acid is acutely toxic to humans when ingested, inhaled or when it comes into contact with the body. It is absorbed through the skin and through mucous membranes. Several adverse effects are reported in humans following ingestion, inhalation and dermal and ocular contact with oxalic acid, including vomiting, dysentery, convulsions, coma, kidney and liver damage, heart failure, cerebral oedema, chemical burns of the intestine, gastroenteritis, and death.

The target species for this product is honey bees.

User Safety

A user risk assessment was provided in compliance with the relevant guidelines.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

- This product is highly acidic and corrosive and could cause severe irritation of eyes, oral and respiratory mucosa, irritation of the skin, and contact dermatitis. Inhalation may cause nosebleeds, headaches, and/or vomiting. Avoid inhalation, accidental ingestion and skin and eye contact including hand-to-mouth and hand-to-eye contact.
- Children should not come into contact with this product. Keep children away when preparing and administering this product.
- Beware of bystanders. Avoid all direct contact with the product during preparation, use, cleaning, and disposal.
- Personal protective equipment consisting of chemical resistant gloves, an FFP3 mask, and safety glasses should be worn when handling and applying the product.
- During preparation, handle the product outdoors or in well-ventilated areas.
- When spraying and evaporating, apply product with your back to the wind.
- Remove contaminated clothing immediately and wash before re-use.
- Do not eat, drink or smoke during handling of the product.
- Used measuring devices and empty containers should be thoroughly washed and/or disposed of immediately and not left in the sight and reach of children.
- In case of accidental ingestion, rinse mouth with water and drink plenty of water or milk. Do not induce vomiting.
- In case of accidental inhalation, move to fresh air and rest in a position comfortable for breathing.
- In case of skin or eye contact, immediately rinse thoroughly with water and remove contaminated clothing or contact lenses.
- If skin/eye irritation persists, or if the product has been inhaled or ingested, seek medical advice immediately and show the package leaflet or the label to the physician.
- Wash hands after use.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:
The product is a natural substance, the use of which will not alter the concentration or distribution of oxalic acid in the environment. Oxalic acid is produced by living organisms and, in most environments, is present as oxalate which is readily biodegradable in soil and surface waters. A Phase II ERA was not required.

III.B.2 Residues documentation

Residue Studies

Oxalic acid has a status on the GB MRL (Maximum Residue Levels) list of 'No MRL required' (in bees only). The applicant has provided bibliographical data which show that there is no significant increase of oxalic acid in honey over the natural levels found in non-treated hives, particularly when oxalic acid is applied from late summer onwards, after honey harvest, or in autumn/winter. The applicant has provided robust assurance that use of the product in accordance with the SPC (particularly when spraying) will not result in oxalic acid residue levels in honey in the brood frame which would exceed the natural levels found in honey.

Withdrawal Periods

Based on the data provided, a withdrawal period of zero days for honey are justified. There is an advisory that the product should not be used during honey flow and treatment of honey producing hives should be carried out without honey supers mounted.

IV. CLINICAL DOCUMENTATION

Due to the legal base of the application, the applicant has presented relevant information and data from scientific and publicly available literature to support the pre-clinical and clinical aspects of the product.

IV.I. Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical information describing the pharmacodynamic and pharmacokinetic properties of oxalic acid dihydrate.

In terms of pharmacodynamics of oxalic acid dihydrate, the mode of action against Varroa mites is not fully understood, but it is known that direct contact with the oxalic acid crystals is required for mite mortality. The applicant has provided information to show that the different methods of administration achieve sufficient delivery of the active substance to the bees themselves, and therefore the parasitic mites.

Regarding the pharmacokinetics of the product, the applicant has provided published literature to show that oxalic acid can penetrate the exoskeleton of honey bees. After administration of oxalic acid by trickling, contamination of adult bees was detected at 24 hours, reaching a peak one day later.

Tolerance in the Target Species

Bibliographical data has been provided by the applicant which show that at the proposed doses, oxalic acid is well-tolerated by honey bee colonies, particularly when applied by sublimation. The trickling method poses a greater risk, due to

the unavoidable potential for ingestion of the active substance, because of the sugar-based administration solution.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The information provided by the applicant shows that there are no published reports of resistance to oxalic acid. No mechanisms are identified that may facilitate such resistance developing and it has been suggested that resistance to oxalic acid is unlikely, based on its fundamental role in metabolic pathways. It is recommended to use oxalic acid as part of an integrated pest management system to avoid the potential of resistant Varroa mites.

Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials

The applicant has provided bibliographical data to support the clinical aspects of the product in the three application methods.

Dose Confirmation Studies and Field Trials:

One paper provided by the applicant by Al Toufailia et al., (2015) was considered to be fully supportive for the recommended product dosage of most of the application methods. This was a randomised, controlled, field trial titled “Towards integrated control of Varroa: 2) comparing application methods and doses of oxalic acid on the mortality of phoretic *Varroa destructor* mites and their honey bee hosts” and was designed to determine the efficacy of oxalic acid in killing phoretic mites on adult worker bees.

In this study, trickling, spraying, and sublimation oxalic acid application methods were tested on 110 broodless colonies in early January 2013 in the UK. Honey bee colonies were located in 10 apiaries at or within 20 km of the University of Sussex in southern England. At each site one colony was a control, untreated with oxalic acid or syrup, but opened and inspected in the same way as the treatment colonies. Treatment efficacy was assessed by extracting mites from samples of worker bees collected immediately before and 10 days after treatment, as well as assessing the number of dead mites on the hive floor which was monitored at two-day intervals for 8 days before, and 10 days after treatment. Worker bee mortality was also monitored for 8 days prior to treatment and for 10 days after.

Data were analysed using the SPSS statistical program version 20. A two-way ANOVA was used to test for differences between the effects of oxalic acid application method and dose efficacy against Varroa and side effects on acute

bee mortality. Tukey's post hoc tests were used to compare Varroa mortality and effects on bees between oxalic acid application methods or doses.

Results showed that all three methods could give high Varroa mortality, of 93–95%, using 2.25 g oxalic acid per colony. Of the three application methods, sublimated oxalic acid is considered as the least harmful to the bees.

Weather Dependency
Sublimation is also considered to be the most weather independent treatment method. Studies comparing the different climatic zones in Northern and Central Europe to Southern and Mediterranean Europe, show that the dose-response differs when using the trickling application method. In the winter in Northern and Central Europe, a field trial by Gregor and Planic (2001), titled "Acaricidal effect of oxalic acid in honeybees (*Apis mellifera*) colonies", showed that concentrations of 3.5%-4.2% oxalic acid were efficacious. The aim of this study was to establish whether oxalic acid could be successfully used as an alternative to acaricide when brood is present. Twenty-four colonies of *Apis mellifera* L were located at one site near Vipava, Slovenia with mild Mediterranean climate influence. The study concluded that oxalic acid was highly effective in the broodless period. The same efficacy was seen at higher concentration of 6.0%-6.2% oxalic acid in southern Europe in a field trial by Coffee & Breen (2016) titled "The efficacy and tolerability of Api-Bioxal as a winter varroacide in a cool temperature climate". For a trickling treatment in summer in northern and central Europe, the same higher concentration of 6%-6.2% was required for good efficacy, which was shown in a poster abstract of a field trial titled "Coloss - Seasonal Brood Interruption as an effective measure for Varroa control" by Büchler, et al., (2019).

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 benefit/risk profile of the product is favourable.

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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