DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Calistrip Biox bee-hive strip

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PRODUCT SUMMARY

EU procedure number	ES/V/0433/001/E/001
Name, strength and pharmaceutical form	Calistrip Biox 6,44 g bee-hive strip
Applicant	Laboratorios Calier S.A. Calle De Barcelones 26 Poligono Industrial El Ramassa Les Franqueses Del Valles – 08520 – Barcelona España
Active substance(s)	Oxalic acid
ATC vetcode	QP53AG03
Target species	Bees
Indication for use	Treatment of external parasitosis in honey bees caused by *Varroa destructor*.

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application*	SRP application in accordance with Article 8 of Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018
Date of completion of the original decentralised procedure	12/03/2024
Date veterinary medicinal product first authorised in the Reference Member State (MRP only)	27/03/2024
Concerned Member States for original procedure	PT
Concerned Member States for subsequent recognition procedure	AT, BG, HR, CY, CZ, FR, DE, EL, HU, IT, PL, RO
Withdrawn CMS during subsequent recognition procedure	N/A

*Please be aware that certain parts of the dossier may be varied and consequently be subject to protection of technical documentation – for these and other changes of referenceability to parts of the dossier, please see chapter POST-AUTHORISATION PROCEDURES

1. SCIENTIFIC OVERVIEW

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

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

The VMP 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 VMP was demonstrated according to the claims made in the SPC.

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

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

2.A. Product description

The VMP contains oxalic acid dihydrate 6.44 g (equivalent to 4.6 g of oxalic acid) and glycerol, light liquid paraffin, erucamide as excipients and poplypropylene as plastic support.

The container/closure system is sachet made of laminated polypropylene, containing 2 and 10 strips.

The choice of the formulation is justified.

The VMP is a novel pharmaceutical form (novel extended release product) and its development is adequately described in accordance with the relevant European guidelines.

2.B. Description of the manufacturing method

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

Process validation data on the VMP have been presented in accordance with the relevant European guidelines.

2.C. Production and control of starting materials

The active substance is oxalic acid dihydrate, an established active substance not described in the European Pharmacopeia/National pharmacopeia of a member state/pharmacopeia of a third country. 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 excipients are in conformity with the Ph.Eur. requirements, except for erucamine (in-house). The specifications of the excipients are acceptable.

The proposed container closure system is well justified. The specification of the container's components is acceptable.

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

2.D. Control tests carried out on isolated intermediates during the manufacturing process

Not applicable.

2.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 VMP.

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.

2.F. Stability tests

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the VMP throughout its shelf life when stored under the approved conditions. Data on in-use stability studies are submitted and support the proposed shelf-life period after first opening.

2.G. Other information

None.

3. SAFETY DOCUMENTATION (safety and residues tests)

3.A. Safety tests

Pharmacological studies

The applicant has provided bibliographical data which attributes the acaricidal effect of oxalic acid partly to a sensitivity of the mites to acid pH. Oxalic acid is believed to immobilize calcium, thus impairing the calcium-potassium ratio in mite tissues.

The applicant has also provided bibliographical data which show that oxalic acid is absorbed, distributed and metabolized in bees after topical administration. Oxalic acid dihydrate is externally distributed on the bees through body contact and/or social food exchange (trophallaxis)

Toxicological studies

The applicant has provided bibliographical data which show that Oxalic acid is moderately to highly toxic after a single exposure via the oral route. Repeated dose toxicity studies in rats showed that, oral doses of 2 to 5 g/kg bw/day for 70 days resulted in moderate nephrotoxicity, while subcutaneous injections of 25 to 75 mg/kg bw/day for up to three weeks caused mild nephrotoxic effects. No NOEL is established for oral toxicity.

According to the references provided, in reproduction toxicity studies, doses of 400 mg/kg caused several reproductive effects like abnormal sperm, reduction of litters, and decreased pup weight. Therefore, a NOAEL of 200 mg/kg was retained for reproductive effects. No NOEL could be derived for developmental toxicity but teratogenic effects cannot be excluded.

Oxalic acid is not genotoxic or carcinogenic but it is an ocular and skin irritant. No information on the sensitization potential has been submitted. However, no hypersensitivity reactions have been reported in published literature.

Observations in humans

The applicant has provided information, which show that oral doses of 50 mg/kg bw of oxalic acid in humans were reported to be fatal. However, oxalic acid is present in the human diet and the dietary intake ranges from 5-500 mg (exceeding 1000 mg in vegetarians)

Development of resistance and related risk in humans

The applicant has provided bibliographical data which show that mites that had received consecutive oxalic acid treatments remained susceptible to the acaricide. Several other conclude that the selection pressure should be low due to oxalic acid rapid degradation inside the colony and infrequency of application, compared to synthetic acaricides. Resistant populations to oxalic acid dihydrate have not been reported.

Excipients

Excipients included in the veterinary medicinal product are commonly used in the pharmaceutical industry.

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline, which shows that the main potential routes of accidental exposure are dermal and ocular contact

and the main risks after exposure are associated with the active substance, oxalic acid, which is a dermal and ocular irritant.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the VMP.

Environmental Risk Assessment

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment.

3.B. Residues documentation

Residue tests

No residue depletion study in honey has been performed.
Instead, the applicant provides the results from a study which used an oxalic acid product applied via in-hive strips at a higher dose, where no relevant residue concentrations were detected in honey samples from both treated and untreated hives. Furthermore, as stated in the CVMP MRL Summary report (EMEA/MR/891/03-Final), oxalic acid is occurring naturally in honey with an average content of approximately 200 mg/kg (range 1 mg/kg to 800 mg/kg), and no significant increase in relation to the natural contents was observed following treatment of bees. The intake in European diets was estimated to be in the range of 5 mg to 500 mg/day, occasionally exceeding 1000 mg/day, and the intake in 20 g honey was expected to be in the range of 0.02 to 16 mg. Therefore, theoretical oxalic acid intake via honey resulting from oxalic acid treatment is considered negligible compared to the overall intake of oxalic acid in daily food from other sources. The applicant has also analysed honey acidity from treated and untreated hives confirming that the treatment with CALISTRIP® BIOX at the dose of 2 strips (6.44 g/strip) for 6 weeks does not increase the natural honey acidity and consequently the oxalic acid residues in honey.

Maximum Residue Limits

Oxalic acid is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmacologically active substance	Marker residue	Animal Species	MRL	Target tissues	Other provision	Therapeutic Classification
Oxalic acid	Not applicable	Bees	No MRL required	Not applicable	NO ENTRY	Anti-infectious agent

The excipients are also either allowed substances for which Table 1 of the Annex to Commission Regulation (EU) No 37/2010 indicates that no MRL is required (Glycerol; Paraffin, light liquid) or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product (Polypropylene; Erucamide: for in-hive use only).

Withdrawal Periods

Based on the data provided above, a withdrawal period of zero days for honey, is considered safe for the consumer.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

4.A. Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical to document the general pharmacological effects of OAD regarding pharmacodynamics and pharmacodynamics.

Development of resistance and related risk in animals

The bibliography provided suggests that *Varroa destructor* populations exposed to oxalic acid treatments remain susceptible to this active substance.

However, since the Regulation (EU) 2019/6 states that it is necessary to mitigate the risk of development of antiparasitic resistance to medicinal products for human use and veterinary medicinal products, adequate warnings and precautions appear on the product literature.

Dose determination and confirmation

The applicant has performed a dose determination controlled study to determine the most efficacious and stable formula among two different formulations (with or without glycerol), to assess the best dose of use (5, 7 or 10 g Oxalic acid dihydrate/strip) and also to establish the best treatment schedule of a 6-week treatment (one single treatment of 6 weeks (2 strips/hive/treatment) or two consecutive treatments of 3 weeks each (2 strips/hive/treatment)).

Tolerance in the target species of animals

The information regarding the safety at higher doses than recommended has been taken from the dose determination study of oxalic acid strips for the treatment of Varroa destructor in honey bees under controlled field conditions. It was concluded by the applicant that no adverse effects and no alterations in the social behaviour of the colonies or the flight activity of bees were detected either in the periodic visits, which was considered to be as expected and appropriate for the time of the year in which the study was carried out. The evolution of the brood in the treated colonies was also considered to be without any alteration and in accordance with the time of the treatment.

4.B. Clinical trials

The applicant has conducted a clinical trial carried out in Spain to confirm the efficacy and safety of the oxalic acid strip at the proposed dose of 6.44 g oxalic acid dihydrate/stirp when used for treatment against Varroa destructor in naturally infected honey bees for a period of 6 weeks. The applicant has also contributed 4 supportive field studies carried out under the same protocol out in Spain.

The efficacy results obtained for the group treated for a period of 6 weeks was 90.67% agree with the guideline EMA/CVMP/EWP/459883/2008-Rev.1 where a 90% or higher for mite reduction for non-synthetic substances are required. The applicant concludes that it can be considered that CALISTRIP® BIOX is efficacious when is administered at the reason of 2 strips / hive for a period of 6 weeks. Regarding the safety:

- It is demonstrated proposed dosage regime do not cause an increase in bee mortality.

- The treatment did not affect the oviposition and development of the offspring. Cessation of brood was not detected in any case.

- Treatment with Oxalic acid for 6 weeks have no negative impact on the strength of the colony.

- During the clinical trial, bee colonies did not show symptoms compatible with varroosis or any other disease.

- No adverse effects were detected due to the treatment with the IVP Oxalic Acid at neither of the tested treatments. There was no increase in bee mortality, nor toxic effects on the brood.

- No alterations in the social behaviour of the colonies or the flight activity of bees were detected either in the periodic visits, which was considered to be as expected and appropriate for the time of the year in which the clinical trial was performed.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP 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 VMP for humans and the environment is acceptable.

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

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 VMP.

None.