College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Formivar 60, 60 g formic acid/100 g bee-hive solution for honey bees
Formivar 85, 85 g formic acid/100 g bee-hive solution for honey bees

Created: August 2019

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0265/001-002/MR
Name, strength and pharmaceutical form	Formivar 60, 60 g formic acid/100 g bee-hive solution for honey bees Formivar 85, 85 g formic acid/100 g bee-hive solution for honey bees
Applicant	Andermatt BioVet GmbH Franz-Ehret-Straße 18 79541 Lörrach Germany
Active substance(s)	Formic acid
ATC Vetcode	QP53AG01
Target species	Honey bees
Indication for use	Treatment of varroosis (*Varroa destructor*) and/or tracheal mites (*Acarapis woodi*) on honey bees (*Apis mellifera*).

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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://mri.cts-mrp.eu/veterinary/).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Well established use application in accordance with Article 13(a) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	26 September 2018
Date product first authorised in the Reference Member State (MRP only)	7 June 2018
Concerned Member States for original procedure	AT, HU, PT, SI

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 60% or 85% of formic acid.

The product is a clear colorless solution in bottles of 1 L. The solution is ready to use.

The particulars of the containers and controls performed are provided.

The choice of the formulation is justified.

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

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.

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

C. Control of Starting Materials

The active substance is formic acid 85% m/V, an established substance described in the German Drug Codex / New Recipe Formulation DAC / NRF 33.21 (2011).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

Not applicable.

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 routine 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 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 European guidelines, demonstrating the (in-use) stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data.

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The mode of action of formic acid is due to the inhibition of the respiratory system of the *V. destructor* mite. The respiratory system of the honeybees is also affected by the formic acid vapours in case of an overdose.
The mite *V. destructor* seems to be more sensitive to formic acid than the most sensitive development stage of the honeybee due to their lower buffering and metabolizing capacity. Efficacy of a treatment is determined by the product (CT) of concentration of the formic acid vapours (C) and the exposure time (T). Long-term treatments can be done with lower concentrations of formic acid over a long period reducing the immediate risk to adult bees. Formic acid kills mites present on bees and in the sealed brood. The pharmacokinetics of formic acid in bees is not known.

Toxicological Studies

The applicant has provided bibliographical data which show that formic acid may cause bee mortality (including queen loss) and brood mortality. Formic acid seems to have an effect on oxidative metabolism of mites and bees and may cause cell death in conjunction with metabolic acidosis. Mites may have a higher susceptibility to formic acid due to their relatively larger body surface in relation to respiratory capacity. The safety of treatment of honey bees with formic acid is strongly dependent on the concentration in the air of the hive.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the veterinary medicinal product is corrosive and very acidic (pH <2), therefore the exposure to small amounts (droplets) may result in severe adverse effects. After ingestion, formic acid causes burns in the gastro-intestinal tract and several deaths in humans have been reported after ingestion of formic acid. Formic acid is also corrosive to the skin and eyes. Respiratory distress may occur after inhalation.

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

Environmental Risk Assessment

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

III.B Residues documentation

Residue Studies

The applicant has provided bibliographical data which show that:

- It is difficult to identify formic acid in honey as residue, as formic acid naturally occurs in honey. Formic acid does not accumulate in bee wax.
- Using formic acid as a varroacide in the hives before the honey flow period may involve the risks of residues in extracted honey up to the taste threshold, which ranges from 300 for the light and 600 – 800 mg/kg for dark honey respectively.

- A study towards honey residue levels of formic and oxalic acid over three years showed a significant increase in formic acid in the honey from apiaries which had been treated during the preceding autumn. No increase of formic acid content of honey was observed after formic acid repeated treatments.

  The results of the presented study showed that long-term formic acid treatment in autumn according to the product information will not increase honey acidity above the MRL of the honey regulation.
- A study investigating 138 honey samples from honey bee colonies treated with formic acid showed that formic acid treatment led to high formic acid amounts in honey and food storage and that the covers of the cells are permeable for formic acid vapours. Honey which is open in the bee hive was more affected with formic acid residues than capped honey. Three to four weeks after the treatment the capped honey contained still more formic acid residue and the open honey had a lower content of formic acid due to the dilution of the honey by the winter food.

MRLs

Formic acid is included in Table 13 of Annex II of the Annex to Commission Regulation (EU) No 37/2010, no MRL is required.

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:
- The mode of action of formic acid is by inhibiting cytochrome oxidase by binding to ferric haem iron and it causes metabolic acidosis which may potentiate cellular injury. Circulatory failure leads to further hypoxia and acidosis.
- Formic acid can be inhaled and absorbed through the skin, ingestion leads to almost total absorption and distribution in the body water compartment.
- Elimination of formic acid from the body is slow, through oxidation (mostly in the liver and erythrocytes) or the tetrahydrofolic acid dependent one-carbon pool.

Tolerance in the Target Species of Animals

The applicant has provided bibliographical data to show that:
- A certain correlation between the body surface area and respiratory intensity and the sensitivity against formic acid exists.
- Mite and bee survival was affected by formic acid dose. There was a significant interaction between temperature, dose and species.
- 21 hours after treatment with evaporated formic acid in a concentration of 85% in deionized water cell death was found in cuticula, subcuticular, fat and glandular cells of the haemocoel and fifty hours after formic acid treatment in all tissues of the larvae body excluding the midgut epithelial cells.

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IV.B Clinical Studies

Field Trials

The applicant has provided bibliographical data which show that:

- The effectiveness of 65% formic acid applied via the Illertisser Milbenplatte (short term treatment) is highly dependent on temperature and should therefore be used during spring and autumn.
- Treatment with a Petri dish with a cotton wad saturated in 25 ml of 85% formic acid placed above the comb frames for eight consecutive daily treatments significantly reduced mite infestation compared to an untreated control and efficacy was similar to fumigation with Taktik®. Colony survival was proven using the same treatment scheme for FA in the following year.
- Good efficacy (around 95%) was found and no effect on brood was reported after treatment with 240 g of 70% formic acid in gel for a duration of 15-18 days (single dose).
- Treatment with formic acid using a natural fibre sheating board impregnated with 250 ml of 65 % formic acid placed inside a vented plastic bag in autumn with the relatively low average daily temperature of 12.20°C provided significant, but substantially less control than treatment with Apistan®. The analysis of the amount of formic acid evaporating during the time period of the study indicates that an increase in efficacy may be possible by altering the delivery system to allow for more complete evaporation.
- Slow-release of 300 ml of 65% formic acid on fibreboard in a vented plastic bag. Mite mortality and treatment group survival was not different between the formic acid treatment groups and Apistan® treatment groups.
- Treatment with 250 ml of 65% formic acid gel pads, encased with an impermeable plastic sheating containing regularly spaced holes, in heavily infected colonies resistant against coumaphos and fluvalinate, provided only a moderate mite reduction. The effects on brood during the first treatment week were significant with a clear reduction of the survival.
- Treatment for two days with formic acid fumigation in different doses showed good efficacy against *varroa* and *nosema*, however no effect on *A. woodi* was observed.
- A trial to determine if indoor fumigation of formic acid can reliably control *nosema* disease and *Acarapis woodi* in overwintering colonies showed that *Acarapis woodi* mite prevalence was not affected by formic acid treatment, although mite mortality in treated groups was greater and *Nosema* spp. spore mean abundance was suppressed relative to untreated colonies.
- A study towards the effect of concentration and exposure time on treatment efficacy against *Varroa* mites during indoor fumigation showed that short-term high-concentration and medium-term medium-concentration fumigation with formic acid killed *Varroa* mites, with averages of 93% and 83% mortality respectively, but both treatments also were associated with an increase in worker bee mortality and queen mortality.
- A study evaluating the effect of spring treatment with organic acids (amongst which 35ml of 65% formic acid) against *Varroa* mites showed that in the formic acid treated groups queen loss occurred compared to the control and oxalic acid groups. In the formic acid treated groups higher *Varroa* drop during treatment, smaller *Varroa* populations during summer and lower mite counts in September, compared to the controls was found.

- A comparison of efficacy between formic acid treatment using gel packets and a paperwick dispenser. Efficacy was around 95% for both treatments. The Liebig treatment significantly increased the number of dead bees in the first week.
- Treatment with 50-75 ml of 50% FA per day on four days using formic acid fumigation boards provides insufficient mite mortality for a standalone treatment, although the treatment might hold promise as a tool for beekeepers that need to control mites during the nectar flow.
- Efficacy of formic acid applied weekly with a sheet of cardboard impregnated with 10 ml or 15 ml of formic acid solution (85%) on *Varroa* mortality in capped brood cells of the Africanized honeybees in Costa Rica was 55.6% with 15ml and only 8.4% with 10ml of formic acid.
- Treatment with a maximum dose of 189 g formic acid (approximately 65% gel) resulted in a mite infestation reduction of around 60%, which differed significantly from the control group.
- Comparison between treatments with 200ml of 65% formic acid by slow release (once) or pour-on (5 times weekly) showed that slow release application was more effective and improved colony development when *Varroa* infestation was relatively high. However, when *Varroa* abundance was low, slow release treatment suppressed brood area.

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 (http://mri.cts-mrp.eu/veterinary/).

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 (Application number)	**Section updated in Module 3**	**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	Module 1 updated	4 June 2019