IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Formic Pro

PRODUCT SUMMARY

EU Procedure number	IE/V/0515/001/DC
Name, strength and pharmaceutical form	Formicpro 68.2 g Beehive Strips for Honey Bees
Active substance(s)	Formic acid
Applicant	NOD Apiary Ireland Ltd 5 George's Dock IFSC Dublin 1 D01 X8N7 Ireland
Legal basis of application	Full application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of procedure	11/02/2021
Target species	Honey bees
Indication for use	Treatment of Varroosis caused by *Varroa destructor* in honey bees (*Apis mellifera*).
ATCvet code	QP53AG01
Concerned Member States	AT, BE, BG, CZ, DE, DK, EL, ES, FR, HR, HU, IT, LT, NL, NO, PL, PT, RO, SE, SK, SI, UK(NI)

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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

II. QUALITY ASPECTS

A. Composition

The product contains 68.2 g formic acid per strip and the excipients corn starch, liquid sugar, wood flour, laminated paper containing biodegradable polymers, xanthan gum and potable water.

The container system consists of a polypropylene/aluminium foil/polypropylene laminated sachet containing two strips, placed in a plastic liner (with resealable tape) and packed in a cardboard box with two, ten or thirty sachets.

The product is an established pharmaceutical form 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 at a licensed manufacturing site.
Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is formic acid, an established active substance. 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 has been provided.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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

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 analytical methods has been provided.
Batch analytical data from the proposed production sites has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance has 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 has been provided in accordance with applicable European guidelines, demonstrating the 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 which show that formic acid is a common metabolic intermediate in living cells and can be present as either the acid or the formate anion. Although the mechanisms of action were not specifically studied, it is believed to impair *Varroa destructor* with local effects that are due to the corrosive action of formic acid vapours. In addition, absorbed formic acid may cause acidosis and may impair the mite's energy supply through inhibition of the mitochondrial respiratory chain.
The pharmacokinetics of formic acid in honeybees has not been studied.

Toxicological Studies

Single Dose Toxicity:

The acute toxic action profile of formic acid is predominantly determined by its inherent irritating/corrosive properties. The toxicity values after oral uptake and inhalation in rats suggest low acute toxicity. The signs of intoxication give no evidence of specific systemic adverse effects.
No acute dermal study has been conducted with the acid itself because of its corrosive action. Following acute dermal exposure of the sodium salt, no local irritation and systemic effects were observed.
Following inhalation of formic acid vapours, clinical signs indicated corrosive properties of the test substance, evidenced by the occurrence of corneal opacity and corrosion of the dorsal nose in some cases. Symptoms persisted until termination 14 days after the rats were exposed to 6.6 mg/l or above. There were no changes in animals that survived. Mortalities occurred within 7 days. Inflated lungs and dilated hearts were seen in animals that died; gross pathology revealed no changes in animals sacrificed at termination.

Repeated Dose Toxicity:

Formic acid salts were administered orally in three studies (two in rat and one in pigs) and in one study via the inhalation route in both rat and mouse. The lowest no observed adverse effect level (NOAEL) reported for repeated oral administration to rats was 280 mg formate/kg body weight (bw)/day following a 52 week exposure, based on decreased body-weight gain, gastric hyperplasia and salivary gland hypertrophy. Oral administration of formate to pigs for >300 days showed no signs of adverse clinical or pathological effects up to the highest dose of 301 mg formate/kg bw/day. In the 13 week repeat dose inhalation test in rats, a no observed adverse effect concentration of 64 ppm (122 mg/l) after prolonged inhalation (6 hours/day, 5 days/week) was reported. This was based on histological changes in the nasal region.

Reproductive Toxicity, including Teratogenicity:
A two-generation study conducted in accordance with OECD GL 416 was performed in the rat to investigate effects of sodium formate at doses of 0, 100, 300 and 1000 mg/kg bw/day on reproductive performance. The NOAEL for general, systemic toxicity was 300 mg/kg bw/day for the F0 and F1 parental rats, based on adverse effects on food consumption and body weight gain observed at 1000 mg/kg bw/day. A NOAEL for reproductive and developmental toxicity of 1000 mg/kg bw/day (equivalent to 677 mg/kg bw/day formic acid) based on the highest dose tested was reported.
Two oral teratogenicity studies conducted in accordance with OECD GL 414 were provided, conducted in rat and rabbit. No substance-related embryotoxic or teratogenic effects were observed at concentrations of up to 945 mg/kg bw/d sodium formate in rats, and 1000 mg/kg bw/d sodium formate in rabbits.

Mutagenicity:
Formic acid was assayed for mutagenic potential in *in vitro* studies. There was no evidence of a mutagenic potential of formic acid in vitro. The chemical structure as well as the metabolism of the test substance did not raise concern over genotoxicity occurring *in vivo*. It was concluded that formic acid is not genotoxic.

Carcinogenicity:
Two carcinogenicity studies investigating the effect of a formic acid salt, potassium diformate, were provided. In the 52 week study, the oral NOAEL in the rat was considered to be 400 mg/kg bw/day. Similarly, in the 80 week oral study in mice, the NOEL was considered to be 400 mg/kg bw/day. No evidence of tumorigenic effect in the stomach or other tissue.

Other Studies
No specific tests on endpoints such as immunotoxicity, endocrine, liver and renal function have been conducted. No skin and eye irritation study reports on formic acid itself are available due to the inherent properties of formic acid (strong acid). There was no evidence for a sensitising potential of formic acid (85% solution) in guinea pigs.
Due to the corrosive nature of formic acid, local effects must be expected at all dose levels.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the main risk to humans is irritation via inhalation, dermal or ocular exposure.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment
Phase I
The environmental risk assessment can stop in Phase I and no Phase II assessment is required because formic acid is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment.
Conclusion
Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues Documentation
Residue Studies
The applicant has conducted a residue study investigating the effect of the product on formic acid residues in honey.

MRLs
Formic acid is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as 'No MRL required.'

Withdrawal Periods
In accordance with the guideline on safety and residue data requirements for VMPs intended for minor uses or minor species (EMEA/CVMP/SWP/66781/2005) a "zero" withdrawal period for honey is required. The residues of formic acid in honey were below the acceptable daily intake of 3 mg/kg bodyweight at all timepoints. Based on the data provided, a withdrawal period of zero days for honey is justified.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

A number of studies using the recommended dose in the target species were conducted. The effect of ventilation, temperature and hive volume were examined. Parameters evaluated were bee mortality, colony strength, queen presence/activity, queen supersedure.

Formic acid will initially disturb colony activities and may, within one day of application, result in queen rejection, triggering queen supercedure activities in rare cases. Insufficient ventilation, high ambient temperatures (>29.5°C) and insufficient hive volume have been identified as particular risk factors for build-up of formic acid concentrations beyond easily tolerated levels. Colonies of less than 10,000 bees might be unable to provide sufficient air flow to allow for a tolerable formic acid concentration.

Increased adult bee mortality, brood mortality and/or queen loss have been observed more so in smaller cavity hive designs or where entrance reducers were not removed prior to use. Secondary signs including bees absconding, reduced reproduction and/or total colony loss have been noted. Disturbing the colony during the treatment period may increase the risk of brood and/or adult bee (including queen) mortality, and absconding.

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

Resistance

The information provided suggests that resistance to the local acid irritation/corrosion effects are extremely unlikely to develop as these are physical processes, while development of resistance to the systemic acidosis and respiratory chain inhibition effects are also unlikely as these effects occur in all cells with more than one enzyme system involved.

IV.B Clinical Studies

Laboratory Trials

A formic acid release rate study was conducted on the product and the authorised product MAQS. No significant difference in release rates of formic acid between the two products was observed over a 14-day period when exposed to room temperature conditions and oven temperatures in simulated beehive environments. Given that the effect of the product on varroa mites is directly related to exposure of formic acid in the air within the beehive, it can reasonably be concluded that a similar rate of release of formic acid between the product and MAQS should result in a similar level of efficacy (both in terms of intensity and duration) against varroa mites.

Field Trials

The applicant has conducted a number of field studies investigating the efficacy of formic acid strips on *Varroa destructor* in honey bees. The studies provided have investigated different durations of treatment, namely two strips applied together for seven or fourteen days. For comparison purposes, the authorised product MAQS Beehive Strips was also included in many of the studies.

The applicant has conducted two field studies investigating the release rate of formic acid from the product as well as the efficacy against varroa mites in which the product was compared to the authorised veterinary medicinal product MAQS as control (both products are comprised of strips containing 68.2 g formic acid). In the first study, two strips of each product were applied during high and normal temperature conditions, peak temperature 33°C and 26°C, respectively. Formic acid vapour levels in the brood chamber air were measured using air sampling tubes for formic acid over a seven day period (high temperature) or eleven day period (normal temperature). Formic acid vapour levels reported in the untreated hive ranged from 0.5 to 5 ppm. There were no differences in formic acid concentration between single and double brood chamber hives. Under high temperature conditions, formic acid levels had almost returned to naturally occurring levels by day 7. In contrast, formic acid levels remained above 20 ppm eleven days after application when used at lower temperatures. The release rate of formic acid was comparable between the Formicpro and the control product (MAQS). A comparable efficacy of 94.7% and 99.1% was reported for Formicpro and MAQS, respectively.

In another study, brood chamber formic acid levels were measured following application of two strips of MAQS (single brood chamber hives only) or Formicpro for a period of 14 days. The two products showed a similar rate of formic acid release, with concentrations in excess of 20 ppm observed for up to 10 days but not at 14 days. An increase in mite fall was observed following treatment with formic acid strips when compared to the placebo group. A single application of two strips of the product for fourteen days demonstrated an average efficacy of >95%. This compared favourably with the product MAQS which also reported efficacy of >95%.

The available bibliographic and efficacy data supported an efficacy threshold for formic acid of 20 ppm.

The treatment period for the single application of two strips for 7 days reflects the higher levels of formic acid observed in the brood chamber of hives during the first seven days of several of the studies, where formic acid levels >20 ppm generally occurred.
To further support the efficacy of the product, studies conducted with the applicant's other product MAQS authorised for the treatment of varroosis caused by *Varroa destructor* in honey bees were also submitted. Both products contain the same concentration of formic acid and are to be used as 2 strips per hive for 7 days. It was concluded that a similar rate of release of formic acid between Formicpro and MAQS are expected to result in a similar level of efficacy (both in terms of intensity and duration) against varroa mites.
Although a number of other studies provided with the application reported a lower efficacy (<90%), it was accepted that in those studies, the lower efficacy observed may be attributed to the challenges associated with controlling extraneous variables in field conditions in honey bee studies such as infestation from untreated control hives due to looting and mite drift, leading to placebo modality collapse at the time of critical treatment due to ongoing excessive varroa loads. In addition, excessive mite numbers prior to study commencement and the delay in applying the critical treatment has also been identified as contributing factors to failure to achieve efficacy >90% in some studies.
In accordance with CVMP Guideline on veterinary medicinal products controlling *Varroa destructor* parasitosis in bees (EMA/CVMP/EWP/459883/2008) and in view of the fact that this application should be considered in conjunction with the guideline on Efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species (MUMS) (EMEA/CVMP/EWP/117899/2004), the data provided is considered adequate to support the efficacy of the product.

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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. 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 HPRA website.
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.

Changes:
None.