IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Bayvarol 3.6 mg Bee-Hive Strips for honey bees

PRODUCT SUMMARY

EU Procedure Number	IE/V/0472/001 (formerly UK/V/0227/001)
Name, Strength, Pharmaceutical Form	Bayvarol 3.6 mg Bee-Hive Strips for honey bees
Active Substances(s)	Flumethrin (85%)
Applicant	Elanco GmbH Heinz-Lohmann-Strasse 4 27472 Cuxhaven Germany
Legal Basis of Application	Full application (Article 12(3) of Directive No 2001/82/EC)
Target Species	Honey bees
Indication For Use	For the diagnosis and control of flumethrin sensitive Varroa jacobsoni in honeybees
ATC Code	QP53AC05
Date of completion of the original mutual recognition procedure	12 October 2006 (UK)
Date product first authorised in the Reference Member State (MRP only)	July 1992 (UK) September 2006 (IE)
Concerned Member States for original procedure	Ireland (now RMS) Spain, UK added via RMS change

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 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. Composition

The product contains the active substance Flumethrin (85%), 4.23mg per strip and excipient low density polyethylene.
The container/closure system consists of four strips packed in a heat sealed polyester/aluminium/polyethylene laminate pouch. The particulars of the containers and controls performed have been 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.

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 using conventional manufacturing techniques.

C. Control of Starting Materials

Flumethrin (85%) is an established active substance and 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.

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

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

E. Control on intermediate products

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

F. 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.

G. 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 stability of the product throughout its shelf life when stored under the approved conditions.
The claim of a 6 week stability after broaching is not based on a stability problem with exposed strips, but that the performance of the product is reduced after 6 weeks of use.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has conducted studies which show that Flumethrin (85%) acts by pre- and post- synaptic induction of repetitive action potentials and disruption of anoxal***[1]*** impulses by changes in K+***[2]*** / Na+***[3]*** permeability.
The applicant has also conducted studies which show that absorption through the skin in mammals is minimal. Three studies were conducted to investigate this and the animals were dosed orally in all studies. The first study showed that flumethrin was

metabolised by the hydrolysis of its central ester bond to form permethrin acid and 3-phenol-4-fluorobenzyl alcohol. The other two studies were conducted using cyfluthrin, which is a similar compound. These showed that urinary metabolites were provisionally identified as conjugate of 4'hydroxy-3-phenoxy-4-fluocrobenzoic acid. They also showed that the major residue in tissues was unchanged cyfluthrin, but there was extensive metabolism in kidney and to a lesser extent in liver and heart muscle. As a result a pathway for metabolism of cyfluthrin was proposed

Toxicological Studies

The applicant has conducted laboratory studies which show that flumethrin is a slight irritant to skin when used as a pour on, but non-corrosive and non-irritant on contact with eyes. There was also no ulcerative dermatitis, foetotoxicity, teratogenic effects, genotoxic effects, and no carcinogenic effect.

- Single Dose Toxicity

Flumethrin is of low acute oral toxicity and the main symptoms observed were with the central nervous system (reduced motility, respiratory disturbances, altered gait, and salivation), typical of x-cyno pyrethroids. The 1% pour-on formulation was virtually non-toxic following dermal[4] application of up to 50mg flumethrin/kg bodyweight (bw) to intact and broken skin. In a test for dermal irritancy/corrosivity the 1% formulation of flumethrin pour-on was slightly irritant (reversible) and non-corrosive; in eyes it was non-irritant and non-corrosive.

- Repeated Dose Toxicity

Flumethrin was administered orally in three studies and was mixed with powdered food and normal feed. The study lasted for 13 weeks and found that 10ppm (equivalent to 0.7mg/kg bw to 0.8mg/kg bw) was the no-effect level, based on ulcerated dermatitis seen at higher levels. It was also found that a no-effect level of 25ppm in feed (0.00mg/kg bw to 0.94mg/kg bw) can be assumed on skin changes.

- Reproductive Toxicity, including Teratogenicity:

Two studies were conducted where flumethrin was administered orally to pregnant animals. It was found that flumethrin was not teratogenic at doses of up to 2mg.kg bw, and at 1mg/kg bw there was a no-effect level for foetotoxicity. In the second study it was found that the no-effect level for foetotoxicity was 1.7mg/kg bw due to a slight but not statistically significant reduction in foetal weights at 6 mg/kg bw.

- Mutagenicity

Flumethrin was assayed for mutogenic potential in *in vitro* studies. It was concluded that flumethrin is not genotoxic.

- Carcinogenicity

A 24-month study was conducted which was a combined chronic toxicity and carcinogenicity study. The flumethrin used in this study was not identical to that used for Bayvarol strips, but it was a very similar substance. It was administered orally in feed, and it was found that there were no compound-related increases in the incidence of any tumour type nor in the incidence of total tumours. Flumethrin was not carcinogenic under the conditions of this assay. The no-observed-adverse effect level was 10ppm, equivalent to 0.47 and 0.60mg/kg bw per day.

Other Studies

The applicant has conducted an additional study administering flumethrin orally and this showed there was no evidence of any neurotoxic damage in animals examined after 14 days of treatment.

Observations in Humans

The applicant has not submitted any data as the product does not have any anti-microbial properties.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that there is a minimal operator hazard from handling the strips, and operator warnings have been agreed. These are listed below.

- Wash hands after handling the strips, before meals and after work.
- When using, do not eat, drink or smoke.
- Do not open the foil bags until immediately prior to use.
- Avoid the strips coming into contact with honey to be harvested for human consumption.

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

Ecotoxicity
The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the greatest risk to the environment from Bayvarol Strips is the disposal of the strips. Warnings regarding the disposal of the product are therefore required, and are listed below.

Flumethrin is dangerous to fish. Do not contaminate ponds, waterways or ditches with the strip or used packaging.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation
Residue Studies
Residue depletion studies using the final formulation have been conducted in bees. Samples of honey and beeswax were taken from hives at several time points. Results show that residues depleted to below the Maximum Residue Limit (MRL) in honey and beeswax before the end of the withdrawal period.
The analytical method was high performance liquid chromatography (HPLC). The method was fully validated.
MRLs
Flumethrin is listed in Annex I for bovines and ovines, and II for honeybees of Council Regulation 2377/90 (O.J. No. 2377/90). The marker substance is flumethrin.
Withdrawal Periods
Based on the data provided above, a withdrawal period of zero days for honey in bees is justified.
[1] Part of a nerve
[2] Potassium
[3] Sodium
[4] Skin

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Pharmacology
The applicant has provided information to show that flumethrin is a type II synthetic pyrethroid, and causes a long-lasting prolongation of the normally transient increase in sodium permeability of the nerve membrane during excitation, resulting in lasting periods of repetitive nerve firing. This causes initial excitement then paralysis.
Tolerance in the Target Species of Animals
The applicant has submitted a number of references of studies for target animal tolerance using multiples of the recommended dose in the target species, bees. A placebo was used as a control. All studies involved the strips being suspended into spaces between the combs in the central brood-rearing area.
Parameters evaluated were mortality, breeding activity and behaviour.
No adverse effects were seen.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance
The information provided suggests that flumethrin resistance appears to be sporadic, with no reported flumethrin resistance in one European country. Bayvarol strips may continue to have value in the diagnosis of the presence of mites.
Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials
The applicant has provided bibliographical data which show that Bayvarol impregnated partitions, rather than an impregnated grid below the combs or a cover above the combs, is the most efficacious way (99% over 27 days) of administering Bayvarol to bees. Various strip arrangements, contact areas and concentrations of flumethrin have also been studied. It was determined that by doubling the number of strips to 4 per colony increased efficacy from 81.9% to 99.7%, even with low concentration strips. Therefore efficacy was shown to be dependant on both flumethrin concentration and contact area. The most

efficacious combination in normal colonies was 4 strips containing 3.6mg flumethrin hanging between the combs in the central brood rearing area. In nuclei and young colonies, 2 strips were more efficacious.

Field Trials

The applicant has provided bibliographical data which show that Bayvarol can be used directly after the last honey harvest. It protects the winter bees from preimaginal damage, which results in the development of physiologically weakened bees in the late summer, therefore losses induced by infestation by Varroa mites over the winter months can be reduced.

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.