Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

PolyVar Yellow 275 mg bee hive strip

Date: 26 April 2017

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0161/01/DC
Name, strength and pharmaceutical form	PolyVar Yellow 275 mg bee-hive strip
Applicant	Bayer Vital GmbH Kaiser-Wilhelm-Allee 70 51373 Leverkusen Germany
Active substance(s)	Flumethrin
ATC Vetcode	QP53AC05
Target species	Honey bee (*Apis mellifera*)
Indication for use	For the treatment of varroosis in honey bees caused by flumethrin sensitive *Varroa destructor* mites

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original Decentralised procedure	25 January 2017
Date product first authorised in the Reference Member State (MRP only)	n.a.
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DK, EE, ES, EL, FR, HU, HR, IT, IE, LU, NL, PL, PT, RO, SE, SI, SK, UK

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. Qualitative and quantitative particulars

The product contains 275 mg flumethrin per strip and the excipients dibutyl adipate, propylene glycol dicaprylocaprate, epoxidised soybean oil, stearic acid, polyvinyl chloride, titanium dioxide (E171), and iron oxide yellow (E172).

The container/closure system is a polyester/aluminium/polyethylene foil bag.

The product is a bee-hive strip to be applied to beehive entrances as a gate; 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 on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

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

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

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 site have been provided demonstrating compliance with the specification.

F. Stability

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 product throughout its shelf life when stored under the approved conditions.

G. Other Information

None.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant briefly describes the pharmacodynamics of flumethrin: it prevents the inactivation of voltage-gated sodium channels by almost irreversible binding, leading to repeated neuron activation associated with prolonged depolarisation.

In addition, pharmacodynamics effects of Flumethrin on different vital functions were tested in rats, mice, guinea pigs and dogs. It was concluded that flumethrin exerts minimal pharmacological effects in the mammalian system (slight reversible increase of glucose levels, a decrease intestinal motility and a moderate effect on motility in mice observed in high dosages). There were no specific secondary pharmacological effects on hematology, diuresis, the immune system as well as the cardiovascular and respiratory system. Flumethrin showed no effect on the nervous in rats but increased the motility at high dosages in mice.

Three studies investigating the pharmacokinetics of flumethrin in rats were presented in the dossier: the oral ADME study in rats showed that absorption of flumethrin commenced rapidly, but incompletely. The highest concentration was found in the blood. The concentrations in tissues were distinctly lower. Of all the tissues, the liver contained the highest concentrations, whereas the lowest concentrations were found in the CNS which indicated a low blood-brain barrier penetration. The main metabolites in rats, in cattle and in sheep were the parent substance and Bayticol acid. The absorption of flumethrin was very low after dermal application in cattle, in sheep and in dogs.

Furthermore, toxicokinetic was evaluated during the subacute (4 weeks), chronic (15 and 19 weeks) and 2-generation rat toxicity. The results obtained from the rats in the dose groups showed a clear dose-concentration relation. The highest concentrations were found four hours after dosing. The results for male animals were usually higher than for females.

In a study where flumethrin was given intravenously or orally to rabbits, oral bioavailability of flumethrin was found to be 60.9%.

Toxicological Studies

The applicant has provided bibliographical data which show that flumethrin-isomer trans-Z2 has an acute oral toxic potential (LD50: 10 to 50 mg/kg bw), whereas the trans-Z1 is of low oral acute toxicity in rats (LD50: > 5000 mg/kg bw in male and > 500 mg/kg bw in female rats). It is an inhalative toxicant. The dermal toxic potential was considered to be moderate .

Repeated dose toxicity of flumethrin has been studied in laboratory animals via oral and dermal exposure between 2 and 15 weeks. Main target organ was the skin. A NOEL of 0.7 mg/kg was observed in male rats, corresponding to 10 ppm, based on ulcerative dermatitis at doses of 2.9 mg/kg and higher. In dogs, a NOEL of 0.88 mg/kg per day (25 ppm) was determined. The overall NOAEL of dermal toxicity was 10 mg/kg body weight and 80mg/kg for skin effects.

Flumethrin was tested in two-generation studies in rats. Data on reproductive toxicity gained from 2-generation studies in rats show NOELs in the range of 0.5-3 mg/kg. Maternal toxicity and effects on foetuses, mainly based on maternal toxicity, were observed. Flumethrin was considered to be not teratogenic in rats and rabbits.
In addition, the mutagenicity of flumethrin has been investigated in the full range of in vitro and in vivo tests in mammalian and bacterial systems. The overall conclusion is that flumethrin has no mutagenic or genotoxic potential in mammalian cells.
No carcinogenic potential was observed in rats and mice.
Furthermore, no immunotoxic or primary neurotoxic properties and no specific effects on the endocrine systems were seen.

Toxicity studies with the formulation on skin exposure were submitted: a very low acute dermal toxicity was observed. The product was not skin irritating nor skin sensitizing. Due to the physical characteristics of the product acute oral, inhalation or eye irritation potential was considered negligible.

The excipients are widely used, for example, in the cosmetic and/or human and veterinary pharmaceutical industry or are permitted as food additives. Used in the product they do not represent a consumer safety concern.

Observations in Humans

The applicant has provided bibliographical data on poisoning due to pyrethroids: the main adverse effect of dermal exposure is paresthesia. Mainly the face is affected and the paraesthesiae are exacerbated by sensory stimulation such as heat, sunlight, scratching, sweating or the application of water. Pyrethroid ingestion gives rise within minutes to a sore throat, nausea, vomiting and abdominal pain. There may be mouth ulceration, increased secretions and/or dysphagia. Systemic effects occur 4-48 hours after exposure. Dizziness, headache and fatigue are common, and palpitations, chest tightness and blurred vision less frequent. Coma and convulsions are the principal life-threatening features.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. Data of a study on “Determination of the exposure of beekeepers to flumethrin beegates 2.5% by fixing them to beehives” showed that handling of the product is safe for the beekeeper and the risk of potential exposure and subsequent adverse effects can be considered negligible. Therefore, standard warnings and hygiene measures listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

Phase I

A Phase I environmental risk assessment (ERA) was submitted in compliance with the guideline CVMP/VICH Topic GL6 - Guideline on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products - Phase I (CVMP/VICH/592/98-FINAL). According to the respective decision tree the assessment can stop in Phase I at question no.14. Entry to the terrestrial environment is prevented as the treatment is only stipulated for bees by bee-hive strips. Therefore, no further assessment is required.

Conclusion

The active substance flumethrin is a well-known synthetic pyrethroid, which might be harmful for aquatic organisms. Therefore, an appropriate disposal advice is included in the SPC and package leaflet.

It can be expected that the product will not enter the environment when used according to the SPC.

III.B Residues documentation

Residue Studies

The applicant has conducted one GLP-compliant field study in the target species honey: Honeycombs were obtained from different test sites in Germany (4 apiaries), Hungary (2 apiaries), Spain (2 apiaries) and The Netherlands (3 apiaries) after application of Polyvar Yellow (flumethrin bee-hive gate).

The maximum application time at hive entrance of 4 months is covered by data from Germany (122 or 120 days) and the Netherlands (119 days). In the other regions application time was 92 days (Spain) and 102 days (Hungary).

Samples of honey and wax were pooled to one honey and one wax sample per apiary and analysed for concentrations of flumethrin based using a validated LC-MS/MS method.

Residue concentrations in honey were below the limit of quantification of 3 µg/kg and also below the lowest calibration standard which corresponds to 1 µg/kg. Concentrations in bees wax were above the LOQ of 25 µg/kg in three out of 11 samples.

MRLs

The active ingredient of the intended product Polyvar Yellow is included in Table 1 of Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin.
An ADI (Acceptable Daily Intake) of 1.8 µg/kg body weight/day (108 µg/person/day) was set.
The MRL status of the Flumethrin is as follows:

Pharmacologically active substance	Marker Residue	Animal Species	MRL	Target tissue	Other provisions	Therapeutic classification
Flumethrin	Flumethrin (sum of trans- Z-isomers)	Bovine	10 µg/kg 150 µg/kg 20 µg/kg 10 µg/kg 30 µg/kg	Muscle Fat Liver Kidney Milk	No entry	Antiparasitic agents/agents against ectoparasites
		Ovine	10 µg/kg 150 µg/kg 20 µg/kg 10 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consump-tion.	
	Not applicable	Bees	No MRL required	Not applicable	No entry	

All further ingredient have an MRL status either being considered as not falling within the Scope of Regulation (EC) No. 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin (EMA/CVMP/519714/2009–Rev.33) to be otherwise excluded from needing a specific MRL.

Withdrawal Periods

Based on the data provided above, a withdrawal period of Zero days for honey from treated bees is justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

The active substance of PolyVar Yellow, flumethrin, is well known and has a marketing authorisation for the treatment of varroosis in honey bees as a strip for in-hive use for over 20 years in many European countries. The proposed veterinary medicinal product introduces a new treatment concept where the active ingredient is in a PVC matrix in the form of strips with holes which is fixed at the hive entrance. Honey bees have to pass the holes when entering or leaving the hives so that bees get exposed to the active ingredient through contact with the “gate”. This product is intended to be used after honey flow during late summer/autumn for up to 4 months.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics
The applicant briefly describes the pharmacodynamics of flumethrin: it prevents the inactivation of voltage-gated sodium channels by almost irreversible binding, leading to repeated neuron activation associated with prolonged depolarisation.

Pharmacokinetics
PolyVar Yellow beegate is a solid strip containing flumethrin, with holes of 7mm in diameter. This strip is placed in the hive entrance in a manner that bees leaving or entering the hive have to pass through one of the holes, thereby getting into contact with the active substance. The applicant has submitted two studies in which information on the pharmacokinetics of flumethrin when used in PolyVar Yellow could be gained from. The studies are exploratory in nature but indicated that flumethrin is transferred to bees passing through a hole in the strip, and is also transferred from bee to bee within the hive.

Tolerance in the Target Species of Animals

The applicant provided literature describing the acute contact toxicity of various varroicides on honey bee adults, and one related study. Additionally, one study on the impact of beehive gate placebo strips on undertaking efficiency by honey bee colonies was presented. The results indicate that the results for the toxic standard is within the acceptable range and the undertaker activity of the colony is not considered disturbed by the beegates.

The studies presented, including dose determination and dose confirmation studies as well as the field study, allow for an assessment of the relevant aspects of bee safety, including the safety for worker bees on the colony level, bee reproduction safety parameters, queen safety, long term observations on colony strength and honey production. There is no indication for a negative impact of PolyVar Yellow treatment on any of these parameters.

The product literature accurately reflects the type and incidence of adverse effects which might be expected. Precautionary measures to be taken to ensure adequate hive ventilation during periods of hot weather are adequately described in the product literature.

Resistance

The applicant has submitted an extensive number of references with regard to resistance against pyrethroids/acaricides in *Varroa destructor*. Since the beginning of the 1990s, resistance of mites to pyrethroids has been claimed in different parts of Europe. The main mechanism of resistance towards flumethrin was attributed to a single point mutation in V925 allele associated with an amino acid substitution (L925V). The frequency is low in the Varroa populations of hives. That indicates that the mutation is not universal and may not survive well in local populations in the absence of pyrethroid selection.
The applicant submitted one research report on evaluation of *Varroa destructor* mites surviving treatment with regard to the occurrence of a gene mutation linked with pyrethroid resistance by qPCR. Due to the results derived from the multicenter field study, some resistance data were determined from different areas from Europe. In a field study performed using Varroa destructor-infested honey bee colonies, the genotypes of post-treatment residual mites (≤5% of the mite population since efficacy was ≥95%) were assessed for the presence of resistance-conferring mutations. Mites with a resistance mutation were detected in approximately 50% of the PolyVar Yellow treated colonies and in approximately 64% of colonies treated with another authorised pyrethroid. The mean percentage of homozygous resistant residual mites per colony was approximately 34% in PolyVar Yellow treated colonies and 49% in colonies treated with another authorised pyrethroid. Therefore, treatments should be rotated in order to prevent further selection for resistance.
In conclusion, the risk of resistance development is considered similar to other acaricide products that are authorized and therefore, the risks of application of PolyVar Yellow with regard to emergence of resistance are considered acceptable and the benefit risk ratio favourable.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

None

Field Trials

The applicant has conducted two dose determination studies, three dose confirmation studies and one multicenter field study.

Dose determination studies

The positive controlled, blinded non - GCP studies were conducted in compliance with the principles of the Varroa Guideline at test facilities in Germany and France. The results of both studies demonstrated high efficacy against *Varroa destructor* for both formulations (2% and 2.5% flumethrin). The honey bees tolerated the treatment in all groups very well. Furthermore, the treatment with flumethrin beegates did not affect the overwintering and spring development of the colonies.

Dose confirmation studies

The positive and negative controlled, randomized and partial blinded GCP studies were performed including appropriate numbers of colonies in compliance with the principles of the Varroa Guideline at test facilities in Germany or the Netherlands. Only one of the three studies could be used for the evaluation of efficacy, since to inadequate infestation rates (<300 mites/colony) in one and resistance/reduced sensitivity of mites against flumethrin in the other study. However, the Dutch study demonstrated a statistical significant high efficacy of 2.5% flumethrin bee-hive strips compared to the untreated control group against natural infestation of *Varroa destructor* in honey bees. With respects to counts of dead bees (in one study), queen toxicity and survival rate of colonies, there was no evidence that flumethrin beegate is unsafe for bees for the anticipated treatment period of four months.

Field study

The applicant has submitted an adequate multicenter randomized field efficacy and safety study largely in accordance with the principles of GCP and with the Varroa Guideline. The study were conducted in Germany, Hungary, the Netherlands and Spain and was well developed regarding the inclusion of > 200 colonies, different climatic conditions throughout Europe, beekeeping practices and bee breeds. The overall calculated efficacy was almost 95%. Excluding Spain because of off-label dosing efficacy was 98.2%. Regarding colony strength development, there is no hint for a negative influence of the PolyVar Yellow treatment and it can be concluded that is has been sufficiently demonstrated that treatment does not lead to inacceptable adverse effects on the long term.

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.

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 Medicinal Agencies website (www.hma.eu).

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.

<None>