ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Apistan 10.3% w/w Bee Hive Strip (UK)
Apistan Vet 10.3 % w/w Bee Hive Strip (SE)

PuAR correct as of 20/12/2018 when RMS was transferred to SE.
Please contact the RMS for future updates.

Updated: April 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0403/001/MR
Name, strength and pharmaceutical form	Apistan 10.3 % w/w Bee Hive Strip
Applicant	Vita (Europe) Limited Vita House London Street Basingstoke Hampshire RG21 7PG UK
Active substance(s)	Tau fluvalinate
ATC Vetcode	QP53AC10
Target species	Honeybee, *Apis mellifera*
Indication for use	Control of varroosis (*Varroa destructor* (formerly known as *Varroa jacobsoni)*) in honeybee colonies

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	14 July 2011
Date product first authorised in the Reference Member State (MRP only)	24 March 1998
Concerned Member States for original procedure	Sweden

I. SCIENTIFIC OVERVIEW

Apistan 10.3% w/w Bee Hive Strip is authorised for use in the honeybee, *Apis mellifera.* The product is intended to be placed in the hive for the treatment of varroosis (*Varroa destructor*, formerly known as *Varroa jacobsoni).* The product contains tau fluvalinate 824 mg per strip. The product is supplied in an interior laminated foil pouch containing 10 strips; contained in an outer pouch bearing the product label. The recommended dosage is 2 strips per brood chamber per beehive. The duration of treatment is 6-8 weeks, after which time the strips must be removed and disposed of. The treatment period should be kept as short as possible in order to reduce the likelihood of trace residues in broodwax and to avoid the development of mite resistance. The efficacy is maximised if the product is used in late summer after the main honey harvest. However, the product can be used at any time of year in case of severe infestations.

The product was first authorised in the UK in March 1998. 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[1]. 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 the active substance tau fluvalinate and excipients polyvinylchloride, bis (2-ethylhexyl) phthalate, butylbenzyl phthalate, epoxidized soybean oil and stearic acd.

The product is presented in an interior laminated foil pouch holding 10 strips; contained in an outer paper pouch.

The choice of formulation is justified.

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

[1] Summary of Product Characteristics

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.

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

C. Control of Starting Materials

Tau fluvalinate is an established active substance and is manufactured in accordance with the principles of GMP[2].

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.

Adequate specifications have been provided for the excipients. This is considered acceptable.

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

Scientific data have been provided and 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.

E. Control on intermediate products

Not applicable.

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.

G. Stability

Active substance:
Data have been provided which indicate that the active substance is stable when stored in the appropriate container under appropriate conditions. The retest period of two years is justified.

[2] Good Manufacturing Practice

Finished product:
Data have been provided which indicate that the finished product is stable for 3 years when stored away from direct sunlight.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Special precautions for storage:

- Keep strips in original, unopened packaging until ready to use.
- This veterinary medicinal product does not require any special temperature storage conditions.
- Protect from direct sunlight.
- Store in original packaging only.
- Do not store strips near pesticides or other chemical substances which could contaminate the product.
- Store away from foodstuffs.
- Replace unused strips in the original packaging.
- Use strips for one treatment only - do not re-use strips.

Shelf-life:

- Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Tau fluvalinate contains an α-cyano group and therefore belongs to the type II pyrethroids which differ from Type I pyrethroids in the kinetics of sodium channel effects and in the spectrum of neurological effects produced in laboratory animals. The mode of action is based on changes in the time-course of opening of voltage-dependent sodium channels of nerve membranes causing prolonged depolarisation and hyperexcitability.

The applicant conducted studies which indicated that absorption from the digestive tract of racemic fluvalinate varies between 30-80% in rats, rhesus monkeys and mice. The metabolism of racemic fluvalinate after oral administration is similar to that of other type II pyrethroids. It involves ester bond cleavage and subsequent hydrolysis and oxidation steps to form phenoxybenzoic acid derivatives and anilinic acid derivatives which are excreted as conjugates in the urine. Another study showed low dermal absorption (5-22%) of racemic fluvalinate in acetone in rats.

Toxicological Studies

Single Dose Toxicity
Acute oral toxicity of tau fluvalinate following oral administration by gavage in corn oil was characterised by LD^{3}_{50} values of 150-350 mg/kg body weight in rats and mice. Side effects resembled the CS-syndrome (choreoathetosis, salivation, pawing, burrowing, tremor and clonic seizures), characteristic of type II pyrethroid effects.

The acute dermal toxicity of fluvalinate in rabbits was low (LD_{50}> 20 g/kg body weight) with little percutaneous absorption following application to shaved abraded skin. Similar results were obtained for racemic fluvalinate applied to intact shaved skin of rats. Local irritation was observed in both species. Signs of toxicity were irritation, ataxia, salivation and decreased body weight. No mortalities were observed.

Repeated Dose Toxicity
Data provided showed that repeated dosing of fluvalinate caused whole body shaking, abnormal stance, pawing, lacrimation, irritability, abnormal cage position preference and irritability on handling in rats receiving the higher doses. In dogs, racemic fluvalinate caused histological abnormalities only for the skin and liver hyperplasia at the higher dose.

Reproductive Toxicity
A 2-generation reproduction study was conducted in rats with racemic fluvalinate. No adverse substance-related effects were observed at a dose rate of 0.5 mg/kg body weight/day. Teratogenicity studies in rabbits with tau fluvalinate administered orally on days 6 to 18 of gestation showed some teratogenic and foetotoxic potential at a maternally toxic dose of 125 mg/kg body weight/day.

Carcinogenicity and Mutagenicity
Suitable references were submitted which indicated that tau fluvalinate is neither carcinogenic nor mutagenic.

Special Studies
A dermal sensitisation study in guinea pigs with tau fluvalinate was provided. Under the conditions of study, tau fluvalinate was non-irritant and exhibited no potential to produce dermal sensitisation.

User Safety

The following warnings and precautions are listed on the SPC and product literature:

- This product can cause skin and eye irritation.
- Avoid contact with skin, mouth and eyes.

[3] Lethal dose

- Wear gloves when handling strips.
- Wash hands thoroughly with soap and water after handling strips or contaminated clothing.
- Do not smoke, drink or eat during application.

Ecotoxicity

The applicant provided an environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.
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

Withdrawal periods:

- Honey: zero days.
- Do not use during honey flow.
- Do not extract honey from the brood chamber.
- Do not harvest honey when the treatment is in place.
- To avoid accumulation of residues in wax, brood frames should be replaced with new foundation on regular basis.
- Do not recycle wax from treated colonies for use as foundation in brood or honey frames.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Tau-fluvalinate is an ectoparasiticide of the cyano-pyrethroid class of compounds, which act by causing rapid depolarisation of the axonal membranes. The molecule is of low toxicity to honeybees in particular due to the poor fit of the molecule in potential receptor sites in this species. In Varroa destructor, uptake is rapid and death results from hyper-excitability and nervous exhaustion.

Tau-fluvalinate acts by contact. Molecules of the Active Pharmaceutical Ingredient migrate to the strip surface at a proscribed rate, determined by the reservoir loading of the polymer. Bees walk over the strips and pick up surface molecules of tau-fluvalinate. Varroa mites in contact with the bees are subjected to the molecule, which is lethal to mites but of relatively low hazard to bees.

The resistance mechanisms of Varroa mites to tau-fluvalinate can be explained by an increased detoxification due to the monooxygenases in the P450 system. Oxygenases appear to be important for the resistance of Varroa mites to tau-fluvalinate, whereas the influence of esterases appears to be negligible. Other mechanisms, such as the reduced uptake of active substance or modification of the binding site, could also be involved.

Pharmacokinetics

Although the target species for APISTAN is the honeybee, the product acts directly upon the Varroa mites associated with the bees. There are no known pharmacokinetic effects in the bees.

Tolerance in the Target Species of Animals

Tau-fluvalinate is a lipophilic compound which can accumulate in wax over repeated administrations. Therefore brood frames should be replaced with new foundation on a regular basis to avoid accumulation of residues. In addition, wax from treated colonies must not be recycled for use as foundation in brood or honey frames.

Both the experimental studies and long field experience indicated that Apistan 10.3% w/w Bee Hive Strip is likely to be well tolerated by bees when used as recommended.

The rate and amount of compound released was dependent on the concentration of fluvalinate in the strip and various concentrations of flavulanate were used in tolerance studies. In cage experiments, it was found that 10% fluvalinate was tolerated by bees, whereas 20% strips produced 60% mortality. In such cages there were limited space and the bees had more frequent contact with the active ingredient than in a hive. In flight cages, it was found that use of 30% strips did not lead to increased mortality.

In clinical dose confirmation studies, there was no increase in bee deaths associated with Apistan 10.3% w/w Bee Hive Strip treatment. There was no apparent effect on honey production in the studies.

Resistance

Tau-fluvalinate resistance has been observed in some populations of *Varroa*. Therefore, where feasible, it is recommended to conduct appropriate testing (eg. Vita/NBU test or Beltsville test) to determine whether resistant mites are present prior to treating the colony.

It is recommended to monitor mite-fall before and after administration of the product to determine the effectiveness of the treatment, particularly when it has not been possible to conduct resistance testing prior to the treatment of the colony.

It is not recommended to use the product in colonies where mites are known to be resistant to another pyrethroid treatment (e.g. flumethrin), since cross-resistance typically occurs.

The product should be used as part of an Integrated Pest Management programme. It is recommended to alternate use with non-pyrethroid varroacides where possible.

IV.B Clinical Studies

Data from general dose action studies, dose determination studies and dose confirmation studies were provided. The studies carried out with fluvalinate solutions sprayed on bees infected with *Varroa* mites indicated that concentrations of 0.6 to 120 ppm were generally 100% effective. Other studies where fluvalinate was applied by micro-diffuser in a bee cage showed that concentrations of 0.01 to 0.5% were 100% effective against *Varroa* mites, but had little or no effect on the bees themselves. The cage tests were carried out with PVC[4] strips impregnated with different concentrations of fluvalinate. These tests indicated very high mite mortality even with concentrations of 0.5 and 1%, but 100% activity was only achieved with 5 to 30% concentrations.

The dose determination studies showed that two 5% fluvalinate strips per hive were 93% effective, whereas five 5% strips, or two 10% strips, were >99% effective against *Varroa* mites on bees. Strips containing 20 and 30% fluvalinate did not generally produce higher efficacy rates. With regard to duration of treatment, efficacy was >99% when two 10% strips were left in the hive for only three weeks.

The dose confirmation studies showed the mean efficacy rate for Apistan 10.3% w/w Bee Hive Strip to be greater than 99% and, even where there was a high pressure of infection, an average of between 94.8% and >99% of mites were killed. Similar results were achieved irrespective of the duration of treatment (between 3 and 8 weeks), geographical or climatic differences and in the three most important varieties of European honey bee. The wide distribution of the trials, and the treatment of different varieties of bees, ensured that efficacy was determined under varying field conditions.

The studies submitted showed that the product was effective against the control of varroosis cited in the SPC.

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.

[4] Polyvinylchloride

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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