FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
AGENCE NATIONALE DU MEDICAMENT VETERINAIRE
8 rue Claude Bourgelat –
Parc d'activités de la grande Marche –
Javené – CS 70611 –
35306 FOUGERES

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Apivar 500 mg Amitraz Bee-hive strips for honey bees.

DATE: 19/10/2017

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0319/001/MR
Name, strength and pharmaceutical form	APIVAR 500 mg Amitraz Bee-hive strips for honey bees [AT, BG, CY, DE, EL, FR, HU, LT] APIVAR 500 mg Bee-hive strips for honey bees [HR, IE, UK] APIVAR [DK] APIVAR vet 500 mg Bee-hive strips [SE]
Applicant	VETO PHARMA 12-14 avenue du Québec – Z.A. Courtaboeuf 91140 VILLEBON-SUR-YVETTE FRANCE
Active substance(s)	Amitraz
ATC Vetcode	QP53AD01
Target species	Honey bees
Indication for use	Treatment of varroosis due to *Varroa destructor* sensitive to amitraz in honey bees

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	application in accordance with Article 13(a) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	26/07/2017
Date product first authorised in the Reference Member State (MRP only)	21/04/1995
Concerned Member States for original procedure	AT, BG, CY, DE, DK, EL, HR, HU, IE, LT, SE, 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 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. Composition

The product contains 0,5 g of amitraz and ethylene vinyl acetate as excipient.
The packaging of the finished product is as described on the SPC. The particulars of the containers and controls performed are provided and conform to the regulation.
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.
Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is amitraz, an established active substance described in the British Veterinary Pharmacopoeia. 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.

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

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.
Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

G. 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.

H. Genetically Modified Organisms

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that amitraz is a formamidine acaricide that acts as an agonist on octopamine receptors causing an over-stimulation of octopaminergic synapses in acari, resulting in tremors, convulsions, detachment and death of the parasite.

Amitraz is delivered at the surface of the strips and acts by contact with bees. The pharmacokinetics of amitraz in bees is unknown.

Toxicological Studies

The toxicological profile of amitraz was assessed by the CVMP, JMPR and EPA and the applicant has provided bibliographical data and conducted an oral extended one-generation reproduction study in rats.

The acute toxicity of amitraz and its metabolites is moderate to low in laboratory species.

Repeated dose toxicity studies in laboratory species showed that the dog was the most sensitive species,

In all cases, the principal sign of toxicity was CNS depression.

In oral reproduction studies with rats, mice and rabbits, amitraz interacted with sexual hormone storage and led to a longer cycle length prolonged estrus, diestrus and proestrus periods and had adverse effects in fertility of male mice.

In a GLP oral extended one-generation toxicity study is rats conducted by the applicant, no effects on reproductive performance and no neurological signs were shown in F0 and F1 generations up to the highest tested dose of 7.5 mg/kg.

Amitraz and its metabolites did not show any genotoxic potential.

Bibliographic carcinogenic data with amitraz showed an increase in incidence of lymphoreticular tumours or of hepatocellular carcinoma in female mice only.
No carcinogenicity was reported when rats received orally 10-13 mg amitraz/kg/day for 2 years.
Hence, the increased incidence of hepatocellular and lymphoreticular tumours in female mice was not considered to be significant to human health.

Other Studies

In GLP studies, amitraz was not irritating for the skin and eyes of rabbits. Amitraz had no sensitising properties but induced a delayed hypersensitivity after topic or intradermal application.
In a GLP study, amitraz did not impair the immune system of rats when orally administered up to 8 mg/kg.

Neurotoxicity data showed that amitraz decreased the motor activity at low doses (1 mg/kg) and affected the visual evoked potential at intermediate (50 mg/kg) and high doses.

Observations in Humans

Amitraz is not used as human medicines. However, the applicant has provided bibliographical data on pharmacological/pharmacokinetic in human. Main adverse effects after ingestion are transient and reversible and consisted principally in moderate to severe CNS depression. After dermal contact, erythematous rash was observed. After inhalation of vapours, erythematous rash on face, conjunctival and upper respiratory irritation may occur.

An ADI of 0.0003 mg/kg was established by EMA. This is similar to the ADI determined by JMPR.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that, considering the low margins of exposure, a risk exists in the case of oral ingestion or ocular contact.
However, 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 topic GL6. According to the respective decision tree the assessment can stop in Phase I.

However, as amitraz may be harmful for aquatic organisms, an appropriate disposal advice is included in the SPC and package leaflet.

III.B Residues documentation

Residue Studies

Residue depletion studies using the final formulation have been conducted in honey bees, propolis, wax and pollen. Samples were taken from honey products at several time points.

MRLs

The active substance, amitraz, is included in table 1 of the MRL regulation 37/2010, as follows,

Marker residue	Animal Species	MRL	Target Tissues	Therapeutic Classification	Regulation
Sum of amitraz and all metabolites containing the 2,4-DMA moiety, expressed as amitraz	Bovine	200 µg/kg 200 µg/kg 200 µg/kg 10 µg/kg	Fat Liver Kidney Milk	Antiparasitic agents/ Agents against ectoparasites	37/2010 of 22.12.2009
	Ovine	400 µg/kg 100 µg/kg 200 µg/kg 10 µg/kg	Fat Liver Kidney Milk		
	Caprine	200 µg/kg 100 µg/kg 200 µg/kg 10 µg/kg	Fat Liver Kidney Milk		
	Porcine	400 µg/kg 200 µg/kg 200 µg/kg	Skin + fat Liver Kidneys		
	Bees	**200 µg/kg**	**Honey**		

The MRL status of excipients of the product APIVAR is indicated in the following table.

Excipient	MRL status
Copolymer of ethylene and vinyl acetate	Out of scope as Poly(ethylene-vinyl acetate)

The composition of the product APIVAR is acceptable according to the European Regulation 470/2009.

Withdrawal Periods

Based on the data provided above, a withdrawal period of zero days is justified with the following recommendations:

Do not use during honey flow.
Do not extract honey from the brood chamber.
Do not harvest honey when the treatment is in place.
Brood combs should be replaced with new foundation at least every three years.
Do not recycle brood frames as honey frames.

IV. CLINICAL ASSESSMENT (EFFICACY)

Tolerance in the Target Species of Animals

The tolerance of amitraz and of the product was assessed in several studies:
These studies showed:

- the absence of impact on bees' mortality, on development of hives and on hive production up to 3 times the recommended dose applied for up to 10 weeks;
- the absence of adverse effects after exposure to up to 4 strips of APIVAR (twice the recommended dose) for 6 weeks;
- a tendency to colonies clustered on very hot days after exposure to 5 times the recommended dose.

Current pharmacovigilance data confirmed the good tolerance of the product when applied at the recommended dose.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The bibliographical information provided suggests that there are some suspicions but no certainty concern regarding the emergence of varroa resistance to amitraz, therefore adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

The applicant has provided bibliographical data which show that amitraz at different doses was used on honey bees and/or *Varroa destructor* as an active ingredient in a solvent or in a formulated product different from APIVAR. Amitraz was applied on the mite using different techniques (topical delivery, spraying, or by the mean of Petri dish with a medium containing amitraz). Amitraz was also applied to honeybees infested with mites (by spraying or evaporation) or in the colonies (by spraying).

Field Trials

The applicant has conducted 7 studies under field conditions with the final formulation of the product: 3 dose determination studies and 4 dose confirmation studies. Some of those studies were recent and some others less recent, *i.e.* already submitted at the time of first approval in France in 1990s. Thus most of studies were performed in accordance with either the superseded guideline for veterinary medicinal products controlling *Varroa jacobsoni* (now *Varroa destructor*) and *Acarapis woodi* parasitosis in bees (first adopted in September 1991, reference 7AE16a) or the guideline on veterinary medicinal products controlling *Varroa destructor* parasitosis in bees (adopted in November 2010, reference EMA/CVMP/EWP/459883/2008). All those field trials were performed in naturally infested bees with *Varroa destructor* with the treatment applied in the hive as recommended in the product literature, *i.e.* strips placed between the head of 2 frames. The applicant also provided efficacy data from literature.

Dose determination studies consisted in a GCP single-centre positive controlled field trial performed in France using 3 different doses, a non-GCP single-centre positive controlled field trial performed in France using only 2 different doses and a non-GCP single-centre positive and negative controlled field trial performed in United States. The dose of 500 mg amitraz per strip and the use of 2 strips per brood chamber were the selected dose for APIVAR, based on use during springtime for 6 weeks according to the 2 studies conducted in Europe (France). The third study confirmed the dose (2 strips of 500 mg amitraz each per hive with a single brood chamber) and the duration of 6 weeks during springtime in U.S.

Three dose confirmation studies were provided to support the treatment duration of 6 weeks. The 2 first studies (France and U.S.) were performed in the presence of a low amount of brood and efficacy above 95% as required by the guideline was confirmed at the recommended dose of 2 strips per beehive for 6 weeks. Considering the third study conducted in Spain the level of efficacy of 95% was not reached after 6 weeks due to the high level of brood at the time of the study (start of treatment in June).

One dose confirmation study was provided to support the 10-week treatment duration if brood is present. This last study was performed according with GLP principles in 2 French apiaries and the efficacy percentage exceeded 95%.

A list of published efficacy tests performed in Europe with the commercial product (France, Italy) was also submitted, including the different tests conducted in France by FNOSAD* since 2007, revealing an efficacy percentage superior to 95% as required by the Guideline.

As a result, the dose of 2 strips per beehive is recommended for 6 weeks if brood is not present or at its lowest level, and for 10 weeks if brood is present.

In addition, as the safety and efficacy of the product has only been investigated in hives with a single brood chamber (dose of 2 strips per hive/brood chamber), the use in hives with more than one brood chamber is not recommended.

** FNOSAD= Fédération Nationale des Organisations Sanitaires Apicoles Départementales (a National beekeeping association federating all local working groups for Bee Health in France)*

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

Procedure Type	Procedure Number	Details	Determined
RUP	FR/V/0319/001/E/001 CMS: Repeat Use: BE, CZ, FI, NO, PL, RO, SI, SK First Use: AT, BG, CY, DE, DK, EL, HR, HU, IE, LT, SE, UK	No change to the SPC or package leaflet after the first marketing authorisation	28/02/2018