College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Thymovar

April 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0120/001/MR
Name, strength and pharmaceutical form	THYMOVAR, 15 g bee-hive strips for honey bees
Applicant	Andermatt BioVet GmbH Franz-Ehret-Str. 18 79541 Lörrach Germany
Active substance(s)	Thymol
ATC Vetcode	QP 53 AX 22
Target species	Honey bees *(Apis mellifera)*
Indication for use	Treatment of varroosis on honey bee (*Apis mellifera*) due to Varroa mite (*Varroa destructor)*.

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MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Stand Alone application in accordance with Article 12.3 1 (j) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	24th November 2006
Date product first authorised in the Reference Member State (MRP only)	5th June 2002
Concerned Member States for original procedure	Germany, France and Belgium

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 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 15 g thymol per wafer (quantitative) and the excipients (qualitative) 5.8 g cellulose sponge cloth per wafer

The container/closure system consist in a sealed airtight double sachet (160 x 460 mm) of a SiOx coated PE foil, each sachet containing twice five wafers.

The choice of the formulation is justified.

The product is a novel 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 on the product have been presented in accordance with the relevant European guidelines.

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C. Control of Starting Materials

The active substance is thymol, which is described in the European 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.

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.

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 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.

The claim of a stability is based on the demonstration of stability for batches broached and stored 4 years below 30 °C.

G. Other Information

Shelf-life of the finished product as packaged for sale: 4 years
Shelf-life after first opening of the immediate package: use immediately.

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III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has conducted studies which show that thymol may directly act on the mite through inhalation or diffusion by damaging structures at different unknown locations (the nervous system of the mite may be affected).

The applicant has also conducted studies which show that concentration > 5 μg thymol / l air in the bee hive kills the phoretic mites on the honey bees. The 15 grams of thymol per wafer are sublimated in the beehive over a period of 3-4 weeks (21 to 28 days). Appropriate sublimation of thymol takes place at temperatures between 12°C and 30°C.

After the removal of the wafers the vaporised residual thymol is exchanged by the natural air replacement of the colony. Residues in the wax of the combs will quickly be released out.

Toxicological Studies

The applicant has provided bibliographical data which show that thymol is of low toxicity. At the recommended treatment dose range it is well tolerated by honeybees. No risk for the user, the target animal or the environment is to be expected.

- Single Dose Toxicity

LD50/doses: 980 mg/kg: rat (oral).

LD50/doses: 640 mg/kg: mouse (oral).

LD50/doses: 110 mg/kg: mouse (intraperitoneal).

LD50/doses: 243 mg/kg: mouse (subcutaneous).

LD50/doses: 100 mg/kg: mouse (intravenous).

LD50/doses: 880 mg/kg: guinea pig (oral).

- Repeated Dose Toxicity

NOEL: rat , 19 weeks, oral feed

NOEL: rabbit , 12 days, oral feed

- Reproductive Toxicity, including Teratogenicity:

rabbit, 1 g/day during 7 days, didn't show any influence on reproduction. There was no macroscopic or microscopic damage in 3 pregnant rabbits and their offspring.

- Mutagenicity

In vivo, oral administration of thymol does not induce micronuclei in mice even in the toxic range (1100 mg/kg bodyweight).

- Carcinogenicity

In mice of the A/He strain, thymol did not increase the incidence of spontaneous lung tumours on repeated injection (total dose up to 6 g/kg body weight; overall duration 24 weeks).

Other Studies

The applicant has provided bibliographical data which show that based on the long history of use, it is reasonable to conclude that no harm will result from exposure to thymol in honey from beehives treated with Thymovar

Observations in Humans

The applicant has provided bibliographical data which show that thymol might have serious effects on the skin (irritation, corrosion, contact dermatitis). These effects occur at higher concentrations. Acute dermal toxicity is very low and inhalation of low concentrations of thymol is not considered harmful.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that skin contact should be avoided because of corrosion and contact dermatitis. Therefore, gloves are mandatory when handling the product.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The product THYMOVAR® contains 15 g of thymol per sponge cloth. Thymol is a phenolic monoterpene which occurs naturally in essential oils of plants and herbs.

Following the guideline in force (CVMPA'ICH/592/98-Final [1]), a phase I assessment is not compulsory because the product is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment.

III.B Residues documentation

Residue Studies

The applicant has provided bibliographical data using radiolabelling which show that four procedures of a gas chromatographic method to determine residues of eucalyptol, camphor, menthol and thymol in honey, beeswax and bee food have been proposed.

No information was provided on duration and conditions of storage of the honey samples in each study and the stability of thymol in the honey samples during storage.

MRLs

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No MRL for thymol has been established.

Withdrawal Periods

Based on the data provided above, a withdrawal period of 0 days for honey is justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data to show that, like other essential oils, thymol is effective in controlling varroa mites. Thymol is thought to act on the octopaminergic nerve system, which is only present in non-vertebrates.

Tolerance in the Target Species of Animals

The applicant has conducted a controlled target animal tolerance study using multiples of the recommended dose in the target species. An authorised reference product containing the same active substance was used as a control. All doses were administered to honey bees, in "Segeberger" styrofoam hives. 12 colonies in one-chamber hives; 13 colonies in two-chamber hives. .

Parameters evaluated were dose-confirmation study, including a positive and a negative type of control. Testing of the efficacy of thymol at lower temperatures in Styrofoam hives.

No negative effect was observed with up to 3 wafers.

Resistance

No data are available regarding the mode of action of thymol.

IV.B Clinical Studies

Laboratory Trials

The applicant has provided bibliographical data which show that under field conditions Thymovar can be effective in the treatment of varroosis due to *Varroa destructor*.

Field Trials

The applicant has provided bibliographical data which show that:

- A clear difference in efficacy between products was observed. Apilife Var and Thymovar showed a very high treatment success in one-chamber hives as well as in two-chamber hives. Apiguard appeared to be increasingly less effective in larger hives.

- The efficacy of Thymovar, oxalic acid and formic acid was studied in 2002 -2003 and 2002-2003. In 2002 - 2003 formic acid and Thymovar were very effective and oxalic acid was less effective. In 2003 – 2004 Thymovar was again very effective, but formic acid was less effective and oxalic acid treatments were very effective.

- Ten hives were treated with Thymovar according to the instruction. One wafer was used for 21 days and then replaced by another one for again 21 days. As final treatment perizin and oxalic acid were used to assess the efficacy of Thymovar. Thymovar was well tolerated by bees and the brood.

- Five colonies were treated with Thymovar, Thymovar was placed on the frames. Fluvalinate was used as a control. The mites were counted daily. The efficacy was 95.3 -97.1% and Thymovar was well tolerated by bees and brood. Immediately after the Thymovar application and during the 3 days following the treatment honeybees appeared nervous with many of them at hive entrance.

- Different methods such as, colonies without brood were sprayed and dripping concentrated sugar syrup with oxalic acid were studied. In some instances a more pronounced winter distress was observed in colonies treated with high oxalic acid-concentrations, but usually they showed a winter-survival, similar to that of the controls.

- The swiss Bee centre tested the spraying treatment on 8 apiaries. The control treatment was carried out with Perizin solution, two weeks after the oxalic acid treatment. There was no significant differences between years, apiaries and types of hives could be determined.

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 Medicines 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.

Summary of change	**Section updated**	**Approval Date**
Repeat Use Procedure – Intended CMS: CY, EL, ES, HU, IT, PT, RO (NL/V/0120/001/E/001)	NA	28th May 2008
Change in the name of the manufacturer of the finished product (NL/V/0120/001/IA/002)	NA	22nd October 2009
Repeat Use Procedure – Intended CMS: CZ, PL, SI, SK and UK (NL/V/0120/001/E/002)	NA	28th April 2010
Change in the name and/or address of the Marketing Authorisation Holder; Replacement or addition of a manufacturer for Batch Release, not including batch control/testing; Change in the QPPV; Change of the site undertaking Pharmacovigilance activities; Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes, update of acronyms, naming changes of functions/procedures). (NL/V/0120/IA/003/G)	Module 1 NA NA NA NA	28th March 2011
Renewal – NL as RMS (NL/V/0120/001/R/001)	NA	16th June 2011
Repeat use – Intended CMS: AT, HR	NA	26th February 2014

(NL/V/0120/001/E/003)		
Deletion of manufacturer responsible for batch release; Change in the QPPV back-up procedure; Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system. (NL/V/0120/IA/004/G)	NA NA NA	25th May 2014
Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH. (NL/V/0120/001/IA/005)	NA	11th January 2017
Renewal – NL as RMS (NL/V/0120/001/R/002)	NA	29th October 2017
Change in the name and/or address of the Marketing Authorisation Holder (MAH); Change of the name and/or address of a manufacturer/importer of the finished product (including responsibility for batch release). NL/V/0120/001/IA/006/G (NL/V/xxxx/IA/035/G)	Module 1 NA	4th June 2019