ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

MAQS Formic Acid 68.2 g Beehive Strip for Honey Bees
MAQS 68.2 g Beehive Strips for Honey Bees (IT)
MAQS (EE)

Date created: August 2014

Updated: May 2018

PuAR correct as of 22/08/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0526/001/MR
Name, strength and pharmaceutical form	MAQS Formic Acid 68.2 g Beehive Strip for Honey Bees
Applicant	NOD Europe Ltd. 5 St Paul's Square Old Hall Street Liverpool L3 9AE
Active substance(s)	Formic acid 68.2 g
ATC Vetcode	QP53AG01
Target species	Honey bee
Indication for use	Treatment of Varroosis caused by **Varroa destructor** in honey bees (*Apis mellifera*).

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	A full Minor Use Minor Species application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	26th March 2014.
Date product first authorised in the Reference Member State (MRP only)	26th February 2013.
Concerned Member States for MRP procedure	Bulgaria, Cyprus, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Portugal, Romania, Slovenia, Spain.

I. SCIENTIFIC OVERVIEW

The MAQS Beehive Strip is formulated for the treatment of varroosis in honey bees (*Apis mellifera*) caused by *Varroa destructor*, a major parasite of the target species, honey bees. The strip contains 68.2 g formic acid, and the dosage 1 sachet (2 strips) per hive. The product was a full marketing authorisation as defined by EMA[1] guidelines provided for Minor Use Minor Species. These applications are relevant where there may be a need for a product in a limited number of target species, or where the need for the product may be for a small number of target species.

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[2]. 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. Of particular note are warnings related to temperature change and the build-up of formic acid. 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.

[1] EMA – European Medicines Agency.
[2] SPC – Summary of Product Characteristics.

II. QUALITY ASPECTS

A. Composition

The product contains 68.2 g formic acid per strip and excipients corn starch, liquid sugar, potable water and laminated paper containing biodegradable polymers. The container system consists of clear, heat-sealed polyethylene terephthalate/polyethylene laminated sachets, each containing two strips, contained in polypropylene tubs of two, three, five or ten sachets. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of formic acid as the active substance, (which also has antimicrobial properties), 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. Process validation data on the product have been presented in accordance with the relevant European guidelines. Preparation is a three-stage process consisting of preparing a gel formation, addition of components and the cutting off of product into strips.

C. Control of Starting Materials

The active substance is formic acid, an established active substance described in the Polish Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice, and a suitable in-house specification from the manufacturer was provided. 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. Suitable declarations and references were included for the excipients.

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

Tests performed during production are described and the results of data, 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 site have been provided demonstrating compliance with the specification. Tests are performed for appearance, mass of individual strip and total formic acid.

G. Stability

Stability data on the active substance, suitable for this type of application, have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Exemption was claimed from providing stability data for the active substance, with a test to full specification being performed before each batch preparation. References relating to the decomposition profile of formic acid were also provided. Three consecutive batches of finished product were tested for suitable parameters. Little change was observed, and the SPC provides suitable warnings with regard to storage.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Store below 25ºC;
- Protect from direct sunlight;
- Store in a dry place;
- Keep the polypropylene tub tightly closed to protect from contamination or product spillage.
- Store in tightly closed original container in a well ventilated area, away from sulphuric acid, strong oxidizing agents (e.g. nitric acid, peroxides, perchlorates, chlorites) and sources of ignition.

Shelf-life of the veterinary medicinal product as packaged for sale: 12 months.
Shelf-life after the first opening of the immediate packaging: use immediately.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

The applicant has provided bibliographical data which show that formic acid is a common metabolic intermediate in living cells, high concentrations of which are toxic. Although the mechanisms were not specifically studied in the target parasite, formic acid is known to act as a respiratory inhibitor via the inhibition of the mitochondrial cytochrome C oxidase complex.

Pharmacokinetics

Published references detailing the pharmacokinetics of formic acid in various species were provided. At physiological pH, formic acid dissociates to formate and a hydrogen ion. Formate is metabolised to water and carbon dioxide via a folate-dependent pathway. Because methanol toxicity is mainly determined by metabolism to formic acid, data on methanol toxicity were also considered. Toxic effects are only expected if the maximum metabolic oxidation rate becomes exhausted (>34 mg/kg bw per day), and thus critical formate blood concentrations are reached. These are reportedly in the range of 8 to15 mM (360 to 680 mg/l). Given the negligible exposure to the beekeeper as the user of the MAQS product (see User Risk Assessment), it is concluded that the pharmacokinetics support the lack of risk in the use of the product according to directed use.

Toxicological Studies

- Single Dose Toxicity

The acute toxic action profile of formic acid is predominantly determined by its inherent irritating/corrosive properties. The toxicity values after oral uptake and inhalation in rats suggest low acute toxicity. The signs of intoxication give no evidence of specific systemic adverse effects.

After acute oral administration of the acid, there was a clear dose-response relationship with respect to mortality and decrease in body-weight gain of survivors. The clinical symptoms and pathological organ lesions were largely unspecific and can be explained primarily by the local corrosive character of formic acid, and associated secondary systemic effects.

No acute dermal study has been conducted with the acid itself because of its corrosive action. Following acute dermal exposure of the sodium salt, no local irritation and systemic effects were observed.

Following inhalation of formic acid vapours, clinical signs indicated corrosive properties of the test substance, evidenced by the occurrence of corneal opacity and corrosion of the dorsal nose in some cases. Symptoms persisted until termination 14 days after the rats were exposed to 6.6 mg/l or above. There were no changes in animals that survived. Mortalities occurred within 7 days. Inflated lungs and dilated hearts were seen in animals that died; gross pathology revealed no changes in animals sacrificed at termination.

- Repeated Dose Toxicity

Formic acid salts were administered orally in three studies (two in rat and one in pig) and in one study (in both rat and mouse) via the inhalation route.

Oral administration of a formic acid salt, potassium diformate, for 13 weeks to rats failed to produce any systemic or target-organ toxicity. Only local irritation caused reversible histopathological changes in the stomach. A local NOEL[3] is less than 600 mg/kg bw per, the lowest dose tested, based on histological changes in the stomach.

Oral administration of a formic acid salt, potassium diformate for 52 weeks to rats failed to produce any systemic or target-organ toxicity. The systemic and local NOAEL[4] was found to be 400 mg/kg bw per day, based on reduced body-weight gain, gastric hyperplasia. and salivary-gland hypertrophy. The LOAEL[5] corresponded to 2000 mg/kg bw per day. Only local irritation caused reversible histopathological changes in the stomach. A local NOEL is less than 600 mg/kg bw per, the lowest dose tested, based on histological changes in the stomach.

Pigs given formate orally for more than 300 days, showed no signs of adverse clinical or pathological effects up to levels of 430 mg/kg per day. Hence, the NOEL is considered to be 430 mg/kg per day.

A 13 week inhalation study showed the upper respiratory tract as the major target for toxicity in rats and mice: incidences of squamous metaplasia of the respiratory epithelium and degeneration of the olfactory epithelium were increased in the high-dose rats and mice. The severity was generally minimal to mild. In mice, body-weight gain was significantly reduced in the high-dose group of both sexes. The local NOEL is considered to be 64 ppm (122 mg/l) in rats, based on histological changes in the nasal region, while the NOEL for systemic effects corresponds to the highest exposure level of 128 ppm (224 mg/l).

A systemic and local NOEL of 64 ppm (122 mg/l) can be established for mice, based on reduced body weight and histological changes in the nasal region.

- Reproductive Toxicity, including Teratogenicity:

Three studies were conducted where sodium formate (a formic acid salt) was administered orally to pregnant animals (rats and rabbits). There was no evidence of teratogenic or embryotoxic effects to arise from the uptake of test-substance up to 1000 mg/kg bw and 945 mg/kg bw in the rabbit and rat studies, respectively.

[3] NOEAL – No observed effect limit.
[4] NOAEL No observed adverse effect limit.
[5] LOAEL – Lowest observed effect level.

- Mutagenicity

Formic acid was assayed for mutagenic potential in *in vitro* studies. There is no evidence of a mutagenic potential of formic acid in vitro. The chemical structure as well as the metabolism of the test substance does not raise concern over genotoxicity to occur *in vivo*. It was concluded that formic acid is not genotoxic.

- Carcinogenicity

Two carcinogenicity studies were conducted which provided clear evidence that there was no carcinogenic potential in rats (20 months) and mice (20 months) dosed with potassium formate (a formic acid salt) in their diet. The NOELs were 50 mg/kg bw per day and 400 mg/kg bw per day, respectively. There is no evidence of a tumorigenic effect in the stomach or any other tissue in either study.

Other Studies

No specific tests on endpoints such as immunotoxicity, endocrine, liver and renal function have been conducted.

No skin and eye irritation study reports on formic acid itself are available due to the inherent properties of formic acid (strong acid). However, the airway irritating properties of formic acid were investigated in mice by measuring the RD_{50} (the concentration of the test material that produced a 50% decrease in breathing rate). The upper airways were irritated and caused a decrease in the respiratory rate of the mice within the 30-min exposure period. There were no deaths in any group. One gross pathological finding was seen during the terminal necropsy which was considered to be of no relevance because similar effects were also seen in unexposed animals. The RD_{50} was determined to be 0.608 mg/l.

There was no evidence for a sensitising potential of formic acid (85% solution) in guinea pigs using the method of Buehler.

Observations in Humans

There are cases of accidental ingestion of formic acid, but the incidence is relatively low. In children, the accidental ingestion occurs generally at low doses, i.e. up to 10 g formic acid, which reportedly caused reversible burns of the pharyngeal tract in 9 children, and all survived. The consumption of only small quantities may be related to the deterrent pungent smell of formic acid.

Oral toxicity
Due to the corrosive nature of formic acid, local effects must be expected at all dose levels. The amount ingested and the concentration used determine the grade and the location of the effects. Therefore, the observations range from moderate burns around the mouth to severe corrosion of the gastro-intestinal tract with destruction of the oesophagus, perforation of the stomach, and corrosion of the small intestine together with massive bleeding and systemic toxicity. Systemic toxicity was seen after ingestion of 30 g formic acid or more.

Skin and eye toxicity
Due to the corrosive nature of concentrated formic acid, local effects must be expected following contact to the skin and to the eyes.

Inhalation exposure
Due to the warning effect of the pungent smell, inhalation exposure of formic acid is generally low. Systemic effects are unlikely to occur due to the high dose required and the deterrent pungent smell of formic acid. The Workplace Exposure Limit (WEL) for air in the UK is 5 ppm *i.e.* 9.6 mg/m³ and is set as a Long-Term Exposure Limit (LTEL) with an 8-hour reference period. This limit is widely accepted and used in many countries. For example, in the USA this limit was adopted as the Permissible Exposure Limit (PEL) in air for formic acid by The National Institute for Occupational Safety and Health (NIOSH) as an 8-hour time weighted average (TWA) concentration, and was based on the risk of severe irritation of the eyes, mucous membranes, upper respiratory tract, and skin.

For the beekeeper as the user of the MAQS product, this workplace exposure limit is extremely unlikely to be exceeded, as exposure to formic acid would be negligible from the proper use of the product according to the label instructions.

Microbiological Studies

Studies in humans
No specific studies in humans have been conducted. However, formic acid naturally occurs in the metabolism of micro-organisms, plants and animals as an intermediate and final product. Under physiological conditions, formic acid is taken up with food, or is formed from small quantities of methanol contained in food or alcoholic beverages, and it is also formed in intermediary metabolism. Therefore, it is unlikely that the negligible additional exposure from the use of the MAQS product would have any impact on human gut flora.

Studies in animals
In Europe, one of the major uses of formic acid is as a silage aid for livestock feed. The formic acid promotes the fermentation of lactic acid and suppresses the harmful formation of butyric acid, while the fermentation processes occur more rapidly and at lower temperature so that fewer nutrients are lost.

In vitro studies
Formic acid has been supported under the Biocidal Products Directive (98/8/EC) as a disinfectant and preservative.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. Due regard was given to CLP Regulation (EC) No 1272/2008 and the corresponding assessment for formic acid. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. The applicant provided appropriate data which supported the safety information for the SPC:

- This veterinary medicinal product is irritating to the skin and eyes. Avoid contact with the skin, eyes and mucous membranes. When handling and applying the product, wear the usual beekeeping protective clothing. Have water readily available.
- In case of accidental eye contact, flush the eye(s) immediately with clear running water for 10 minutes, seek medical advice and show the package leaflet to the physician.
- Avoid contact with skin by wearing chemical resistant gloves (EN 374). In case of accidental skin contact, wash the exposed skin immediately with water and seek medical advice if irritation persists.
- Avoid inhalation of vapour. Only open the product container and unwrap strips outdoors, standing upwind of the product. In case of accidental inhalation move to fresh air and seek medical advice if irritation persists.
- Keep children well away during application of product.
- Do not eat, drink or smoke whilst handling and applying the product.
- Always wash hands with soap and water directly after use.
- People with known sensitivity to formic acid or oxalic acid should administer the veterinary medicinal product with caution.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that as formic acid will be applied to hives, no exposure to terrestrial or aquatic environments will occur. Formic acid is a natural substance and it will be contained within the hive where it will volatilise. There will be no exposure of the terrestrial or aquatic environments. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as recommended:

- Do not contaminate ponds, waterways and ditches with the strip or used packaging. Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

III.B Residues documentation

Residue Studies

The applicant conducted seven residue depletion studies, (one pivotal), using the product in honey bees. For the pivotal study, samples of honey were taken from bees at several time points. The analytical method was the Boehringer Mannheim Formic acid test kit and the method was fully validated.

Withdrawal Periods

Based on the data provided above, a withdrawal period of zero days was set for this product.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Although the specific action of formic acid on *Varroa destructor* is not known, its use as a control on the parasite is well established. A review of the literature regarding the pharmacodynamic effects of formic acid was carried out by the applicant. Formic acid may be present in living cells as the acid or the formate anion. In high doses it is toxic, and acts as a respiratory inhibitor of the cytochrome oxidase complex.

Pharmacokinetics

At physiological pH, formic acid dissociates to formate and a hydrogen ion. Carbon dioxide and water are subsequently formed from the metabolisis of the formate ion via the folate dependent pathway. Methanol toxicity may develop from formic acid metabolism and data were also provided for methanol toxicity. A series of relevant papers were presented for analysis, describing the absorption, distribution, metabolism and elimination of formic acid and potassium diformate.

Tolerance in the Target Species of Animals

The applicant conducted a controlled target species tolerance study using multiples of the recommended dose. Parameters evaluated were temperature and dose concentration. The purpose of the study was to observe the optimum conditions for treatment which would eliminate the target parasite without harming honey bees. The SPC carries the appropriate warning:

- Do not use at temperatures outside the specified range (10 – 29.5°C).

Resistance

Information provided suggests that it is unlikely that resistance in the target parasite is unlikely to occur as any irritation effects are physical in origin and respiratory effects occur within individual cells which contain more than one enzyme system.

IV.B Clinical Studies

Twelve trials were conducted with the product or its equivalent, containing the same concentration of formic acid. The various trials evaluated the use of the product at different points in the life-cycle of the hive and/or the target parasite.
Assessment of efficacy was performed by alcohol washes of bees to remove and count dead mites, sticky boards placed at the bottom of the hive to catch mites falling from bees. The opening of capped cells to determine the status of

mites and larvae was also used, along with an evaluation of mite rebound population to establish the status of surviving mites. Following treatment, a product with known high efficacy was used in order to count any remaining mites not killed by the test product. Tolerance data were also gathered from these trials.

Test 1

This was an initial screening trial using two preparation of 48.4% formic acid, introduced at various doses into hives in order evaluate tolerance and efficacy. One presentation was sachets of gel in 50 g, 100 g, 150 g or 200 g doses. This worked effectively. The other preparation consisted of a gel filled tray, which was not used by the bees and was therefore ineffective. The study was performed over 24 hours or three days. Good results achieved for the 200 g formulation enabled further trials to take place.

Test 2

This trial concentrated on targeting the male mite, based on the premise that if males are killed prior to mating, the female population of the mite would remain low. Twenty-one colonies at a suitable time-point in hive life-cycle, (queen right), and containing sufficient loads of mite were grouped into three sets for a twenty-two day trial. Group 1 received no treatment, group 2 received a 200 g dose of product comparable to the test product, and group 3 received 300 g of test product. Formic acid levels were monitored and mite levels assessed. No adverse effects on the bees were noted. Data were gained with regard to a direction for further trials.

Test 3

This was a report on the efficacy of a comparator product, (University of Hawaii, 2009). Treatment was over three days, and the trial was performed over a month. Forty-one hives were divided into four groups which received 200 g strips with no honey supers on, 300 g strips with no supers, 300 g strips with supers on, and a negative control group. Assessment of mite mortality was performed by analysis of mites on sticky boards every three days, and by observation of larvae and mites in capped cells. Brood damage, queen presence and egg laying activity were monitored as response parameters for hive health, and levels of formic acid were measured. Results reflected good mite kill under the cell cap, and there was no adverse effect on colonies.

Test 4

An assessment of the test product was performed to evaluate the mid-term effects of the product in thirty-nine hives with 48.4% formic acid on target species and target parasite. Treatment groups were group 1 control hives without super, group 2 treated hives with super and group 3 treated hives without super. Treated groups were treated with 3 formic acid strips per hive. Efficacy was evaluated by the use of sticky boards used to trap fallen mites, the use of alcohol washes of bees, and counts of mites in bees. Behavioural

changes in the bees were also noted. Some hives were fitted with a mesh to collect dead bees. The treatment period was three days, and sampling included the analysis of honey, disease analysis of capped cells and adult bees and microscopic analysis of mites taken from bees. No adverse effects from treatment were noted and there was a reduction in the numbers of mites.

Test 5

This trial analysed the efficacy of 48.4% formic acid on the target mite and any side effects on bees in field conditions. A product comparable to the test product was used. Study design consisted of two groups of twelve hives, divided into three treatment groups of four colonies each. Group 1 was an untreated group, group 2 was treated with the test product without a super, and group 3 were treated with the test product plus a super. The test item was applied and removed after four days a control product was then used and removed after ten weeks. The evaluation of efficacy was performed by the use of sticky boards used to trap fallen mites, the use of alcohol washes of bees, and counts of mites in bees. Behavioural changes in the bees were also noted. Although adverse temperature and inherent disease during the time of trial had an effect on bee mortality, valuable data were gained with regard to the efficacy of the product.

Test 6

Groups of twenty healthy colonies were treated for three days with test product plus sugar, test product plus no sugar, or remained untreated. Efficacy was evaluated using sticky boards to catch fallen mites. And analysis performed showed that both treatment groups created significantly higher efficacy than the control group but were not significantly different to each other. Some adverse effects were seen due to high temperature, but valuable data was gained for follow-on studies.

Test 7

Three treatments were performed on a large number of colonies, which included group 1 no treatment, group 2 300 g formic acid or group 3 400 g formic acid. Colony strength, mites on sticky boards, mites on adult bees and in larvae and formic acid residues were all assessed. Super addition and hive size were evaluated as having an effect on efficacy, but the product proved effective.

Test 8

This trial on groups of twelve colonies was performed on group 1, a positive control group using a comparator product, group 2 150 g test product and group 3, 300 g test product. Mites were counted on boards and when taken from bees via appropriate wash or when seen in capped cells. The general health of the queen and brood were also assessed. A further assessment took place in April to evaluate winter mortality and queen status. This trial supported the use of the product at 300 g at lower temperatures.

Test 9

This trial assessed the effect of two application methods of the product on adult bee mortality and colony development, and a comparison of efficacy and formic acid levels in honey under field conditions. Two strips were left in colonies with or without super, or no treatment was given, (ten colonies each). Endpoints measured included measurement of dead bees (Including queen) on specific days, colony development post-winter, mite mortality, bee disease and assessment of formic acid levels. Suitable statistical analyses were performed, and a positive control product was used post-treatment as a critical treatment to attempt to ascertain differences in product effectiveness. No adverse effects were seen from use of the product and although 100% control was not gained with use of the positive control product, possibly due to mite numbers and not a long enough exposure to the product, good efficacy was seen in the test product.

Test 10

This trial tested the product in a commercial bee-keeping situation. The test product was compared to a positive comparator product, with positive results, and demonstrated that the product could easily be used in a commercial situation.

Test 11

This was a tolerance trial, used to confirm the upper temperature limit for use of the product. Suitable warnings appear in the SPC with regard to temperature.

Test 12

A tolerance trial intended to test the resistance of colonies to elevated levels of formic acid was also performed. A standard dose (nine hives) or a double dose (ten hives) of the product was used, with three colonies being used as negative controls. Although a double dose caused some mortality amongst queens was seen, but supercedure was effectively triggered to replace these. Suitable warnings appear 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.

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.

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