IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Ataxxa 200 mg/40 mg spot-on solution for dogs up to 4 kg

PRODUCT SUMMARY

EU Procedure Number	IE/V/0439/001-004 (formerly UK/V/0551/001-004)
Name, Strength, Pharmaceutical Form	Ataxxa 200 mg/40 mg spot-on solution for dogs up to 4 kg Ataxxa 500 mg/100 mg spot-on solution for dogs over 4 kg up to 10 kg Ataxxa 1250 mg/250 mg spot-on solution for dogs over 10 kg up to 25 kg Ataxxa 2000 mg/400 mg spot-on solution for dogs over 25 kg
Active Substances(s)	Imidacloprid, Permethrin
Applicant	KRKA, d.d., Novo mesto Šmarješka cesta 6, 8501 Novo mesto Slovenia
Legal Basis of Application	Hybrid application (Article 13(3) of Directive No 2001/82/EC)
Target Species	Dogs
Indication For Use	For the treatment and prevention of flea (*Ctenocephalides felis*) infestation. Fleas on dogs are killed within one day following treatment. One treatment prevents further flea infestation for four weeks. The product can be used as part of a treatment strategy for flea allergy dermatitis (FAD). The product has persistent acaricidal efficacy against tick infestations (*Rhipicephalus sanguineus* and *Ixodes ricinus* for four weeks, and *Dermacentor reticulatus* for three weeks) and persistent repellent efficacy (*Ixodes ricinus*) for three weeks. Ticks already on the dog may not be killed within two days after treatment and may remain attached and visible. Therefore the removal of ticks already on the dog at the time of treatment is recommended, in order to prevent them from attaching and having a blood meal. This Indication is not applicable to the UK product. One treatment provides repellent (anti-feeding) activity against the sand fly *Phlebotomus perniciosus* for three weeks and against the mosquito *Aedes aegypti* from 7 days up to 14 days after treatment. Reduction of the risk of infection with *Leishmania infantum* via transmission by sandflies (*Phlebotomus perniciosus*) for up to 3 weeks. The effect is indirect due to the veterinary medicinal product's activity against the vector.
ATC Code	QP53AC54
Date of completion of the original decentralised procedure	30 October 2015 (IE) 22 July 2015 (UK)
Date product first authorised in the Reference Member State (MRP only)	Not applicable.

Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain. UK added as CMS via RMS change

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

These were generic 'hybrid' applications submitted in accordance with Article 13 (3) of Directive 2001/82/EC, as amended, assessed via dose confirmation study, as *in vivo* bioequivalence for spot-on products cannot be demonstrated by bioavailability studies. The reference product was Advantix Spot-on Solution for Dogs, marketed in the UK since December 2003. The product is intended for use in dogs, for the treatment and prevention of flea infestation by *Ctenocephalides felis*. Additional claims for the control of ticks are not included in this UK Public Assessment Report, as these are not relevant to the UK. The product can be used as a repellent against the sand fly *Phlebotomus perniciosus* for three weeks and against the mosquito *Aedes aegypti* from 7 days up to 14 days post treatment. The product also reduces the risk of infection with *Leishmania infantum* via transmission by sandflies (*Phlebotomus perniciosus*) for up to 3 weeks. The effect is indirect due to the veterinary medicinal product's activity against the vector.
The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any 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 benefit/risk analysis is in favour of granting a marketing authorisation.
SPC – Summary of product Characteristics.
Efficacy – The production of a desired or intended result.

II. QUALITY ASPECTS

II.A. Composition

The products contain imidacloprid and permethrin as active substances, and the excipients butylhydroxytoluene (E321), triglycerides medium chain, N-methylpyrrolidone, citric acid anhydrous (E330), and dimethyl sulfoxide.
The container/closure system consists of a white polypropylene pipette closed with either a polyethylene or polyoxymethylene cap. Each pipette is packed in a polyethylene terephthalate/aluminium/low density polyethylene triplex bag. A pipette contains 0.4 ml, 1.0 ml 2.5 ml, or 4.0 ml of solution, depending on the product. A box contains 1, 3, 4, 6 or 10 pipettes. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a simple mixing process, followed by filling into pipettes.

II.C. Control of Starting Materials

The active substances are permethrin and imidacloprid. The active substances are manufactured in accordance with the principles of good manufacturing practice. Both active substances are sourced in accordance with an active substance master file.

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. All excipients are monographed within the European Pharmacopoeia.

II.C.4. Substances of Biological Origin
Suitable data were received in line with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process
Not applicable.

II.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.

II.F. Stability
Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Stability data were provided for batches of imidacloprid stored for up to 12 months at 25^{o}C /60% RH and up to 6 months 40^{o}C /75% RH. No adverse changes were noted from these assays or tests on photostability. A retest period of 24 months was agreed.
A retest period of 48 months was agreed after analysis of results for permethrin, batches of which were was stored for up to 60 months at 20^{o}C /60% RH and at 40^{o}C/75% RH for up to 6 months.
Storage and photostability tests were performed on the finished products. Batches filled into each proposed quantity size were stored at 25^{o}C /60% RH for up to 60 months and at 40^{o}C/75% RH for up to 6 months. Based on results, a final shelf-life of 3 years was agreed for the products.

G. Other Information
Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Store in the original packaging in order to protect from moisture and light.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

These were applications for generic hybrid products, according to Article 13 (3), for which *in vivo* bioequivalence with a reference product could not be demonstrated. The results of pharmacological and toxicological tests from published literature were provided.
Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III.A Safety Documentation
Pharmacological Studies
Pharmacodynamics
Permethrin preferentially binds to the sodium channels within the cells of cold-blooded insects, causing a nerve block and eventual death. The active substance does not have the same effect in mammals, which have a different receptor subtype. The mode of action of imidacloprid is mediated via post-synaptic nicotinic acetylcholine receptors. An agonistic effect is caused via selective binding at insect receptor binding sites, as opposed to mammalian sites.
Pharmacokinetics
Permethrin is partially absorbed form the intestinal tract and is poorly distributed among internal organs, but is seen at higher concentrations in fat. The active substance is rapidly metabolised and excreted via the urine and faeces.
Imidacloprid is rapidly and completely absorbed. In dogs, the active substance can be found in the skin epidermis, hair follicles and sebaceous glands up to 4 weeks after administration as a transferable residue. Elimination of the active substance occurs via the urine and faeces.

Toxicological Studies

The applicant provided bibliographical data.

- Single Dose Toxicity

In animal studies using permethrin, it was noted that the LD_{50} is much higher where the *cis:trans* ratio is greater for the *cis* isomer. The vehicle of administration also had impact. The proposed products are designed to give optimal efficacy at optimal dose. Imidacloprid is of low toxicity when applied dermally to mammals.

- Repeated Dose Toxicity

Permethrin

An oral NOEL of 5 mg/kg bw/day was seen in a 52 week study in dogs, and at 1000 mg/kg/day in rabbits. Significant adverse effects noted were increased liver weight, due to microsomal enzyme induction, and neurotoxicity. The SPC states an accepted single dose of 50 mg/kg.

Imidacloprid

In repeated dose studies using imidacloprid, liver changes and reduced weight gain were the most significant adverse reactions observed. For dogs, the lowest NOAEL which was based on disturbances of hepatic function and elevated hepatic microsomal enzyme levels was 15 mg/kg bw/day. Neurotoxic studies generated a lower NOAEL. The SPC states an accepted single dose of 10 mg/kg.

- Reproductive Toxicity, including Teratogenicity

From bibliographical data provided, permethrin is not considered to be toxic with regard to reproduction. Imidacloprid is not considered toxic with regard to Embryotoxicity or teratogenicity, with some effects seen only at doses above maternal toxicity.

- Mutagenicity

The mutagenicity of permethrin was assessed using a battery of relevant tests. Only an *in vitro* test for chromosomal damage gave a positive result, but in isolation, this result was not considered significant in relation to use of the products.
Imidacloprid was tested using a battery of *in vitro* tests. A slight increase in chromosomal aberration rate was noted, but this was not seen as significant. All *in vivo* chromosomal tests were negative.

- Carcinogenicity

No NOAEL that could be translated to humans was identified from rodent studies for permethrin. No carcinogenic effects were noted for imidacloprid in mice or rats in long-term dietary administration. The NOAEL was 100 ppm, equivalent to 5.7, g/kg bw/day according to observed changes in the thyroid.

Studies of Other Effects

Repeat dose neurotoxicity studies in the dog and rat did not identify a NOEL for permethrin. A NOAEL of 300 mg/kg was proposed for use in acute oral exposure scenarios. The active substance is mildly irritating to the eyes and skin, but was not a skin sensitiser when tested by the Magnusson/Kligman method.
From relevant studies, a NOAEL of 42 mg/kg was determined as being the most relevant for acute scenarios of the user risk assessment for imidacloprid. In suitable studies imidacloprid was identified as not being a skin or eye irritant, and is not expected to be a skin sensitiser.

Observations in Humans

For permethrin, toxicity data is limited to dermal exposure. Reversible paraesthesia and mild irritation have been reported at the site of contact up to 12 hours after exposure. Mild contact dermatitis has been noted for imidacloprid.

User Safety

A user risk assessment was provided in compliance with the relevant guideline.
NOAEL were suitably calculated for the worst scenario, namely, interaction with the active substances and children.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- Avoid contact between the product and skin, eyes or mouth.

- Do not eat, drink or smoke during application.
- Wash hands thoroughly after use.
- In case of accidental spillage onto skin, wash off immediately with soap and water.
- People with known skin sensitivity may be particularly sensitive to this product.
- The predominant clinical symptoms that in extremely rare cases may be shown are transient sensory irritations of the skin like tingling, burning sensation or numbness.
- If the product gets accidentally into the eyes, they should be thoroughly flushed with water. If skin or if eye irritation persists, seek medical advice immediately and show the package leaflet or the label to the physician.
- Do not ingest. In case of accidental ingestion seek medical advice immediately and show the package leaflet or the label to the physician.
- Treated dogs should not be handled especially by children until the application site is dry. This may be ensured by treating the dogs in the evening. Recently treated dogs should not be allowed to sleep together with their owner, especially children.
- In order to prevent children from getting access to pipettes, keep the pipette in the original packaging until ready for use and dispose of used pipettes immediately.

Environmental Safety

A Phase 1 environmental study was appropriately submitted in line with relevant guidelines. The product will be given to individual non-food producing companion animals. The SPC and product literature carry suitable warnings.
NOEL – No observed effect level.
NOAEL – No observed adverse effect level.

IV. CLINICAL ASSESSMENT

IV.I. Pre-Clinical Studies

Pharmacology

The efficacy of the products, as cited with regard to the indication in the SPC, was demonstrated via a significant dose confirmation study.

Tolerance in the Target Species

The applicant provided an animal oral toxicity study, and a target animal safety study conducted in accordance with the relevant guidelines, as well as providing published literature in support of this section. The adverse events noted in the oral toxicity study included vomiting, tremors and incoordination, but overall ingestion of 1x dose was well tolerated. In the target animal tolerance study a dose of up to 5x recommended dose was well tolerated. The main effects observed were local skin reactions, including erythema, oedema and alopecia, in addition to scaling and spiking of the hair which were seen in the 1x group. The product literature accurately reflects the type and incidence of adverse effects which might be expected to be seen.

Resistance

No significant resistance data were located for these active substances in a published literature search.

IV.II. Clinical Documentation

Laboratory Trials

The applicant conducted several studies, including a significant dose confirmation study supporting the indication in the SPC. The products contain the same volume and concentration of the active substances as the reference products, and are presented in the same manner. Therefore, efficacy was assessed via dose confirmation studies.

Dose confirmation studies:

<u>NOTE:</u> The product authorised in the UK carries ONLY the indication for C. felis. Claims for indications against Rhipicephalus sanguineus, Dermacentor reticulatus and Ixodes ricinus do NOT apply to the UK-authorised product.

Study title	A dose confirmation efficacy study of a single application of an imidacloprid/permethrin spot-on formulation against induced infestations of *R. sanguineus* and *D. reticulatus* ticks on dogs
Objectives	Confirmation of the target dose effectiveness of the proposed product against artificially induced tick infestation in dogs.

Test site(s)	Single site.
Compliance with Regulatory guidelines	Good Clinical Practice.
Test Product	Imidacloprid 100 mg/ml, permethrin 500 mg/ml spot-on solution as investigational veterinary product (IVP).
Control product/placebo	Untreated control group.
Animals	16 dogs (7 male 9 female) aged greater than 6 months and weighing between 9.8 and 24.1 kg, with established good health. All de-wormed and tick-free prior to the start of the study.
Outcomes/endpoints	Calculated using the following formula: Efficacy against ticks (%) = 100 x ($m_C - m_T$)/ m_C Where m_C = Mean number of live ticks on control animals. m_T = Mean number of live and killed, engorged ticks on IVP treated animals. Arithmetic and geometric means calculated, but the latter were to provide supportive evidence only.
Randomisation	Separated by sex, ranked within sex in order of pre-administration combined species live attached tick counts and then blocked in pairs. Dogs allocated to group one or two within blocks.
Blinding	Partial blinding.
Method	Fifty unfed ticks of each species applied to each dog on days -6, -2, 7, 14, 21 and 28. Ranking for tick retention day -4. Tick counts 48±2 hours post treatment, or non-treatment. Visual assessment of alloscutum. IVP applied at either one location between shoulder blades (dogs < 10 kg), or four location between should blades and base of tail. Animals weighing <10 kg received a 1 ml pipette of the product, animals weighing > 10 kg and < 25 kg received a 2.5 ml pipette of product. Applied only on day 0.
Statistical method	Differences in tick counts between IVP treated and control group estimated using a mixed model analysis of variance for a repeated measures design, with significance set at the 5% level.
RESULTS	
Outcomes for endpoints	There was a significant ($p<0.001$) difference in efficacy between groups on all days, except day 2.
DISCUSSION	Immediate efficacy was not demonstrated. Persistent efficacy exceeding 95% was demonstrated against both tick species (day 9 to day 30). The product was well tolerated when administered at the recommended dose range. The SPC should be referred to for agreed persistency details and any contraindications.

Study title	A dose confirmation efficacy study of a single application of an imidacloprid/permethrin spot-on formulation against induced infestations of *I. ricinus* ticks on dogs
Objectives	Confirmation of the target dose effectiveness of the proposed product against artificially induced tick infestation in dogs.
Test site(s)	Single site.
Compliance with Regulatory guidelines	Good Clinical Practice.
Test Product	Imidacloprid 100 mg/ml, permethrin 500 mg/ml spot-on solution as investigational veterinary product (IVP).
Control product/placebo	Untreated control group.

Animals	16 dogs (8 male 8 female) aged between 12 and 60 months and weighing between 11.1 and 17.2 kg, with established good health. Combed free of ticks on day -10.
Outcomes/endpoints	Calculated using the following formula: Efficacy against ticks (%) = 100 x ($m_C - m_T$)/ m_C Where m_C = Mean number of live ticks on control animals. m_T = Mean number of live and killed, engorged ticks on IVP treated animals. Arithmetic and geometric means calculated, but the latter were to provide supportive evidence only.
Randomisation	Separated by sex, ranked within sex in order of day -5 attached tick counts and then blocked in pairs. Dogs allocated to group one or two within blocks.
Blinding	Partial blinding.
Method	Fifty unfed ticks of each species applied to each dog on days -7, -2, 7, 14, 21 and 28. Tick counts 48±2 hours post treatment, or non-treatment. Visual assessment of alloscutum. Product administered at four locations between shoulder blades and base of tail. Product administered to provide pre-determined doses 0.10, 0.16, 0.20, or 0.25 mL/kg. Applied only on day 0.
Statistical method	Differences in tick counts between IVP treated and control group estimated using a mixed model analysis of variance for a repeated measures design, with significance set at the 5% level.
RESULTS	
Outcomes for endpoints	There was a significant ($p<0.0001$) difference in efficacy between groups on all days.
DISCUSSION	Immediate efficacy was not demonstrated. Persistent efficacy exceeding 90% was demonstrated against both tick species (day 9 to day 30. The product was well tolerated when administered at the recommended dose range. The SPC should be referred to for agreed persistency details and any contraindications.
Study title	A study to determine the efficacy of a single application of a flea treatment (imidacloprid/permethrin spot-on), when compared to an untreated control group against artificially induced flea infestations (*C. felis*)
Objectives	Determination of efficacy when compared to an untreated control group.
Test site(s)	Single site.
Compliance with Regulatory guidelines	Good Clinical Practice.
Test Product	Imidacloprid 100 mg/ml, permethrin 500 mg/ml spot-on solution as investigational veterinary product (IVP).
Control product/placebo	Untreated control group.
Animals	16 dogs (8 male 8 female) aged between 23 and 92 months and weighing between 10.9 and 18.8 kg, with established good health, and combed to ensure no fleas were present.
Outcomes/endpoints	Calculated using the following formula: Efficacy against fleas (%) = 100 x ($m_C - m_T$)/ m_C Where m_C = Mean number of live fleas on control animals.

	m_T = Mean number of live fleas on IVP treated animals. Arithmetic and geometric means calculated, but the latter were to provide supportive evidence only.
Randomisation	Separated by sex, ranked within sex in order of day -5 live attached flea counts and then blocked in pairs. In addition, the eight animals allocated to Group 2 were subdivided into four pairs, one pair for each dose level. Each pair consisted of one male and one female animal. Within blocks, dogs randomly allocated using Fisher and Yates tables into group one or two.
Blinding	Partial blinding.
Method	Approximately 100 unfed fleas (50±15 females and 50±15 males) applied to each dog over a series of days. Flea counts were conducted 48±2 hours post flea infestation and 24 and 48 hours post IVP administration, (fleas were counted *in situ* and remaining fleas left on the animal at 24 hour count). Fleas found by combing for 10 minutes with a flea comb. Animals on which viable fleas were found within this timeframe were combed for a further five minutes.
Statistical method	Differences in flea counts between IVP treated and control group estimated using a mixed model analysis of variance for a repeated measures design, with significance set at the 5% level.
RESULTS	
Outcomes for endpoints	There was a significant ($p<0.0001$) difference in efficacy between groups on all days.
DISCUSSION	Efficacy against *C. felis* fleas was demonstrated and treatment claims were granted. The product was well tolerated when administered at the recommended dose range. The SPC should be referred to for agreed persistency details and any contraindications.

Study title	A study to determine the efficacy of a single application of a flea treatment (imidacloprid/permethrin spot-on), when compared to an untreated control group against artificially induced flea infestations (*C. felis*). A study on dogs immersed weekly in water
Objectives	Determination of efficacy when compared to an untreated control group.
Test site(s)	Single site.
Compliance with Regulatory guidelines	Good Clinical Practice.
Test Product	Imidacloprid 100 mg/ml, permethrin 500 mg/ml spot-on solution as investigational veterinary product (IVP).
Control product/placebo	Untreated control group.
Animals	16 dogs (8 male 8 female) aged between 19 and 76 months and weighing between 10.9 and 17.8 kg, with established good health, and combed to ensure no fleas were present.
Outcomes/endpoints	Calculated using the following formula: Efficacy against fleas (%) = $100 \times (m_C - m_T)/ m_C$ Where m_C = Mean number of live fleas on control animals. m_T = Mean number of live fleas on IVP treated animals. Arithmetic and geometric means calculated, but the latter were to provide supportive evidence only.
Randomisation	Separated by sex, ranked within sex in order of day -4 live

	attached flea counts and then blocked in pairs.
Blinding	Partial blinding.
Method	Approximately 100 unfed fleas (50±15 females and 50±15 males) applied to each dog over a series of days. Flea counts were conducted 48±2 hours post flea infestation, except day 2, when counts were performed 48±2 hours post IVP administration. Fleas found by combing for 10 minutes with a flea comb. Animals on which viable fleas were found within this timeframe were combed for a further five minutes.
Statistical method	Differences in flea counts between IVP treated and control group estimated using a mixed model analysis of variance for a repeated measures design, with significance set at the 5% level.
RESULTS	
Outcomes for endpoints	There was a significant ($p<0.0001$) difference in efficacy between groups on all days.
DISCUSSION	Efficacy against *C. felis* fleas was demonstrated and treatment claims were granted. The product was well tolerated when administered at the recommended dose range. The SPC should be referred to for agreed persistency details and any contraindications. The SPC carries the following information with regard to animals introduced to water: *The product remains effective against fleas if the animal becomes wet. After weekly immersions in water for one minute the period of persistent insecticidal efficacy against fleas was not reduced. However, prolonged, intense exposure to water should be avoided. In cases of frequent and/or prolonged water exposure the persistent efficacy may be reduced. In these cases do not retreat more frequently than once weekly. If a dog requires a shampoo, it should be administered before applying the product or at least 2 weeks after application, to optimise efficacy of the product.*

Field Trials

No data were required for this section.

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 of the product(s) is favourable

VI. 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 HPRA website.
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.

Safety/Efficacy changes

Summary of change (Application number)	**Approval date**
Addition of new indications (repellent activities against *Ixodes ricinus*, *Phlebotomus perniciosus* and *Aedes aegypti)* IE/V/0439/001-004/II/007	October 2021

Addition of new indication - Reduction of the risk of infection with *Leishmania infantum* via transmission by sandflies (*Phlebotomus perniciosus*) for up to 3 weeks. The effect is indirect due to the veterinary medicinal product's activity against the vector. IE/V/0439/A/010/G	December 2022