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CVMP assessment report
Activyl Tick Plus (EMEA/V/C/02234)

Common name: Indoxacarb-Permethrin

Assessment Report as adopted by the CVMP with all information of a commercially confidential nature deleted

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Introduction

An application for the granting of a community marketing authorisation of Activyl Tick Plus was submitted to the Agency on 23 November 2010 by Intervet International BV in accordance with Regulation (EC) No. 726/2004. The product was eligible for the centralised procedure under Article 3.2.(a) of Regulation (EC) No. 726/2004 as it contains a new combination of active substances which has not previously been authorised in the Community.

Activyl Tick Plus is an ectoparasiticide containing indoxacarb and permethrin as the active substances and is presented in cardboard boxes of 1, 4 or 6 pipettes. Activyl Tick Plus is indicated for flea and tick infestations in dogs and may be used as part of a treatment strategy for flea allergy dermatitis. Developing stages of fleas in the pet's immediate surroundings are killed following contact with Activyl Tick Plus treated pets.

The route of administration is spot-on use. The target species is dogs.

Part 1 - Administrative particulars

The bulk manufacture of the finished product is conducted in USA and the product is batch released in the EU from Intervet Productions SA at Igoville in France. The certificates of GMP compliance provided by the MAH were deemed satisfactory.

A Detailed Description of the Pharmacovigilance System that the applicant will have in place has been provided and is considered satisfactory. A statement has been provided by the applicant and the qualified pharmacovigilance person confirming their availability and the necessary means for the notification of adverse reactions.

Part 2 - Quality

Composition

The proposed veterinary medicinal product contains indoxacarb 150 mg/ml and permethrin 480 mg/ml in a non-aqueous solution of propylene glycol monomethylether with the antioxidant propyl gallate.

Container

The product is packaged in single-dose spot-on applicators consisting of a polypropylene/cyclic-olefin-co-polymer/polypropylene blister and an aluminium foil/polypropylene co-extruded lid stock, secondary packed in aluminium sachets. There are five presentations, i.e. 0.5 ml, 1.0 ml, 2.0 ml, 4.0 ml, and 6.0 ml, each with a unique pipette size.

Development pharmaceutics

Indoxacarb, permethrin, propylene glycol monomethylether, and propyl gallate are all well-known pharmaceutical substances, already approved and used in veterinary spot-on solutions for dogs. The choice of the formulation is based on the solubility of indoxacarb and permethrin in several tested solvents and the evaluation of appearance and run-off of the applied solution on the animal in a standard repeatable process. Preservatives are not required in the formulation as the product is for single-use. Development studies have demonstrated that the addition of an antioxidant is required. A clear overview of the products that were used in the submitted clinical and non-clinical studies has been provided. All clinical studies have been done with the proposed commercial formulation. As

preliminary data indicated an increase in water content upon exposure to higher relative humidity environments and photostability studies demonstrated that the product packed in the pipette is not stable in light, an aluminium sachet was added as additional packaging. The product is highly flammable. A warning is included in the SPC under section 4.5.

Method of manufacture

Propyl gallate, indoxacarb and permethrin are dissolved in propylene glycol monomethylether. As a flammability/safety precaution, the tank will be blanketed with nitrogen. The bulk solution is filtered in the filling process. The process is straightforward and considered as a standard process. The fill weight is based on the bulk product density and the previously determined residual volume that will remain in the containers after expression of the dose from the pipettes. Validation on three pilot-scale batches indicates that the manufacturing process yields a robust reproducible product, yet the fill weight will be confirmed in the validation with production scale batches, together with hold times. Full scale validation data regarding the manufacturing process will be provided post-approval for this standard process.

Control of starting materials

Active substance

Indoxacarb is a new active substance, not described in the European Pharmacopoeia (Ph. Eur.), United States Pharmacopoeia (USP) or Japanese Pharmacopoeia (JP). The active substance is the S-enantiomer. An Active Substance Master File (ASMF) has been submitted for indoxacarb. The same version of the open part as currently approved for the approved mono-component product (Activyl) has been provided by the applicant. It is confirmed that the active substance indoxacarb is identical to the active substance used in Activyl spot-on solution (EU/2/10/118/001-004). The information and documentation on this active substance has recently been evaluated within the marketing authorisation application of Activyl spot-on solution. During pre-submission discussions it has been agreed that presentation of indoxacarb information in this marketing authorisation application is not necessary and cross-reference to Activyl spot-on solution is acceptable.

Permethrin is a well-known active substance, not yet described in the Ph. Eur. and not described in the British Pharmacopoeia. An ASMF has been submitted for this active also.

The synthesis has been described in sufficient detail. The process has been evaluated based on three batches. As a re-test period cannot be approved until new stability results are available, the active substance will be used based on testing at the time of use of permethrin. It has been confirmed that permethrin supplied from the same manufacturer, has already been approved for another spot-on product for dogs and concerns the same synthesis, it is acceptable that GMP validation and re-evaluation of specifications will be done post-approval.

Excipients

For propyl gallate reference is made to the Ph. Eur. For propylene glycol monomethylether an in-house specification is applied. That specification is similar to the specification applied for another solution from the same manufacturer and applicant.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Declarations were provided from the active substance manufacturers that no input materials used for the production of the finished product fall within the scope of the guidance 'Note for guidance on minimising the risk of Transmitting Spongiform Encephalopathy agents via Human and Veterinary Medicinal Products' (EMEA/410/01-Rev.2). The finished product is compliant with the Note for Guidance.

Control tests during production

Not applicable.

Control tests on the finished product

Specifications have been set for appearance, identification, concentration of the active substances, related substances and propyl gallate, water content, uniformity of dosage units, and average delivered mass of indoxacarb and permethrin. The average delivered mass is specified and determined by calculation from the concentration of active substances and the average delivered volume per spot-on pipette. The specifications are acceptable and in line with VICH Guidelines. The methods have been described in sufficient detail. Results of batch analysis of three pilot-scale batches confirm compliance to the specifications.

Stability

Based on the 12-month results of stability studies at normal, intermediate and accelerated conditions, a shelf-life of 24 months, stored in the original aluminium packaging to protect from moisture and light is acceptable. The only trend observed is a decrease in anti-oxidant propyl gallate, yet all results amply comply with the set specifications.

Overall conclusions on quality

The dossier provides a detailed description of the active substances and the chosen formulations, and demonstrates that production of the active substances and the products leads to a stable product with consistent quality. In view of the standard production manufacturing process of the drug product and the provided validation data on pilot-scale, full scale validation may be performed post-approval. In general, the analytical methods are well described. Due to the introduction of new methods, a re-test period still needs to be established for permethrin. So far, active substance batches will be tested immediately prior to use. In view of the stability data provided, a shelf-life of 2 years is acceptable for the finished product. A clear overview on the formulations and products that were used in clinical studies has been provided. The administration in the clinical studies is acceptable in view of the method of administration indicated in the SPC. The packaging is as approved for the recently approved mono-component spot-on product from Intervet (Activyl).

Part 3 – Safety

The safety of indoxacarb was considered in the context of the recent application for a marketing authorisation for Activyl. Due to its use for agricultural purposes, the safety of indoxacarb has been studied thoroughly. However, these studies served another purpose, i.e. user and consumer safety rather than safety in the target species. Consequently, differences in study design, implementation and reporting as well as formulations used were observed. Although the information is valid as such,

extrapolation to safety-aspects of indoxacarb in target animal species requires careful consideration of data.

Based on the no observed effect levels (NOAEL) generated with the racemic (50:50) mixture of enantiomers, the purified and the 75:25 ratio of enantiomers in rats (3 months studies), the toxicity of all three materials is quantitatively and qualitatively similar. Effects seen in subchronic 3-month feeding studies in mice and dogs with the racemic (50:50) mixture of enantiomers are qualitatively very similar to those seen in rats, moreover mice appeared less sensitive than female rats.

Adverse events observed in the *in vivo* repeat dose 3-month toxicology studies in rats (at ≥ 4 mg/kg bw per day with purified S-enantiomer) and dogs (at ≥ 5 mg/kg bw per day with racemic (50:50) mixture of enantiomers) were mild haematological effects. This toxicological effect of indoxacarb is mild regenerative red cell haemolysis, which is thought to be the result of oxidative damage to red cells mediated by the putative metabolite N-hydroxyaryllamine IN-MT713. This metabolite contains the structure of the hydroxylated metabolites of aniline, a known substance causing haemolysis (or methaemoglobinaemia). Slight increases in methaemoglobin as well could be seen in rats in subchronic oral toxicity studies with the purified S-enantiomer. Methaemoglobin results from oxidation of haemoglobin iron from the ferrous to the ferric state.

Tolerance studies were carried out in the target species as a spot-on treatment at the recommended dose as well as 3x and 5x overdoses. The minimum age was 8 weeks for dogs. No adverse reactions were observed.

Reproduction toxicity was studied in laboratory animals with indoxacarb and permethrin and has not shown any evidence of a foetotoxic or materno toxic effect at 1.5 mg/kg bw in rats with indoxacarb and at 170 mg/kg bw per day in rats with permethrin. In the developmental toxicity studies no evidence of a developmental or materno toxic effect were observed at 2 mg/kg bw per day in rats and at 500 mg/kg bw per day in rabbits with indoxacarb and at 225 mg/kg bw per day in rats and 1200 mg/kg bw per day in rabbits with permethrin. However, a reproductive toxicity study conducted in the dog at three times the recommended therapeutic dose did reveal a significant reduction in the live pup ratio. The clinical significance of this latter finding is unknown as no studies were carried out in dogs using the recommended therapeutic dose. Therefore, the product is not recommended for use in breeding, pregnant and lactating animals unless based on the benefit/risk assessment of a veterinarian (see section 4.7 of SPC).

The data provided adequately characterise the toxicological profile of indoxacarb.

In support of the pharmacology and toxicology of permethrin the applicant has submitted literature references. These references describe studies carried out over many years and using a variety of permethrin formulations, administered to various animal species.

Permethrin is a well known active substance with recognised efficacy and an acceptable level of safety as it has been used in agriculture and medicine for the control of arthropod infestations for decades.

Adverse effects are known, but the incidence is very low and the use of permethrin can be considered to have an acceptable level of safety. The safety of permethrin has been evaluated by CVMP resulting in the establishment of MRLs in cattle and sheep.

For the dog, permethrin has also been available for use as an ectoparasiticide.
Efficacy and safety are further supported by clinical study data, including tolerance, dose-confirmation and field studies. The applicant has also carried out studies to identify possible pharmacological interactions between indoxacarb and permethrin. No evidence for any interaction was detected.

User safety

Hazard identification and characterisation

For indoxacarb, the applicant refers to the toxicity information that is available in the dossier of Activyl and only a brief summary is provided in the current dossier.

For permethrin, the applicant refers to publicly available literature and databases (e.g. International Programme on Chemical Safety (IPCS), CVMP MRL summary report, World Health Organisation (WHO) evaluation, Registry of Toxic Effects of Chemical Substances (RTECS), Hazardous Substances Databank (HSDB)).

Overview of the toxicity data relevant for the user safety assessment:

	Indoxacarb	**Permethrin**
Acute oral toxicity	low $LD_{50\ rats}$ ≥179 mg/kg bw corn oil $LD_{50\ rats}$ >2000 mg/kg bw Activyl $NOAEL_{rats}$= 12.5 mg/kg bw PEG-400	low $LD_{50\ rats}$ ≥400 mg/kg bw corn oil $LD_{50\ rats}$ >1725 mg/kg bw water $NOAEL_{rats}$= 90 mg/kg bw corn oil
Acute dermal toxicity	low $LD_{50\ rats}$ >2000 mg/kg bw Activyl	low $LD_{50\ rats}$ >2000 mg/kg bw no solvent
Chronic oral toxicity	$NOAEL_{3\ months\ oral\ in\ rats}$ = 1.7 mg/kg bw per day	$NOAEL_{3\ months\ oral\ in\ dogs}$ = 5 mg/kg bw per day
Chronic dermal toxicity	$NOAEL_{28\ days\ dermal\ in\ rats}$ = 50 mg/kg bw per day	$NOAEL_{21\ days\ dermal\ in\ rats}$ = 500 mg/kg bw per day
Endpoints that most frequently defined chronic NOAEL	decreased bw and bw gain, food consumption, and food efficiency	enlarged liver associated with hepatic microsomal enzyme induction
Chronic effect	minimal or mild, reversible increase in red cell turnover (extravascular haemolyses)	enlarged liver
Reproductive toxicity (rats)	no effect on the reproductive performance of parental rats at 6.7 mg/kg bw per day (diet)	oral $NOAEL_{rats}$= 170 mg/kg bw per day (diet) oral $NOAEL_{mice}$= 5 mg/kg bw per day (corn oil)
Embryotoxicity	$NOAEL_{rats}$= 2 mg/kg bw per day (PEG-400) not teratogenic in rats and rabbits	oral $NOAEL_{rats}$= 225 mg/kg bw per day (corn oil) not embryotoxic or teratogenic in rats, mice and rabbits
Mutagenicity	not mutagenic	not mutagenic
Carcinogenicity	not oncogenic in rats, mice and dogs	possible weak carcinogen in rodents, but carcinogenic potential of permethrin is not a cause for concern (EMEA)

The following GLP compliant acute dermal and ocular toxicity tests were performed with a test formulation that was equivalent to the final formulation:

Test	Result	Reference
Acute Dermal Irritation in rabbits	non-irritating to the skin of rabbits	Mallory, 2009
Primary Eye Irritation Study	non-irritating (EEC and GHS criteria) moderately irritating (EPA criteria)	Mallory, 2009
Dermal sensitisation – Maximization Test (Magnusson-Kligman Method) in guinea pigs	non-sensitizer	Mallory, 2009
Transfer rate of indoxacarb and permathrin from treated animals to humans	During the first day after treatment, 1.7 (indoxacarb) and 1.8% (permethrin) of the given dose may be acutely transferred to the user by stroking the treated dog. Between the 1st and 28th day after treatment, 0.56 (indoxacarb) and 0.63% (permethrin) of the given dose may be transferred daily to the user by stroking the treated dog	Wrzesiński, 2010

Based on these toxicity data, the following N(O)AELs should be used in the risk characterisation:

		Indoxacarb	Permethrin
Dermal exposure	acute	154 mg/kg bw	2745 mg/kg bw
	chronic	877 mg/kg bw/day	11150 mg/kg bw/day
Oral exposure	acute	12.5 mg/kg bw	90 mg/kg bw
	chronic	1.7 mg/kg bw/day	5 mg/kg bw/day

The applicant provided toxicity data on the excipients which justifies their inclusion in the formulation as safe.

Propylene glycol monomethyl ether: Propylene glycol monomethyl ether is of low acute and chronic toxicity (oral LD_{50} values are in the range of 5-12 g/kg bw in rodents and dogs and NOAEL in dogs is 1000 mg/kg bw/day).

Propyl gallate: Exposure to propyl gallate is stated to be without concern, because:

- propyl gallate is included in the list of antioxidants allowed for the use as an additive in foodstuffs in the EU (Directive 95/2/EC).
- due to its rapid metabolism and excretion, low acute and chronic toxicity and ready biodegradation
- the US Environmental Protection Agency (EPA) has underlined that aggregate exposure to propyl gallate when used as antioxidant in pesticide formulations will not result in harm to any population
- exposure is low: propyl gallate is present at low concentration (0.02%) in Activyl Tick Plus.

Risk characterisation

The Margins of Exposure (MOEs) have been calculated for all potential relevant exposure scenarios as detailed below:

Scenario		Indoxacarb	Permethrin
dermal exposure by accidental spillage	adult	41	229
dermal exposure after opening the product accidentally	child	15.4	86
dermal exposure after getting accidental access to the used pipette	child	308	1716
dermal exposure by stroking/handling the treated animal on the day of treatment	adult	592	3191
dermal exposure by stroking/handling the treated animal on the day of treatment	child	358	1906
dermal exposure by stroking/handling throughout day 1-28 after treatment of the animal	adult	9744	38448
dermal exposure by stroking/handling throughout day 1-28 after treatment of the animal	child	5847	23229
oral exposure by hand-to-mouth contact when treating the animal	adult	100	226
oral exposure by hand-to-mouth contact when opening the product accidentally	child	4.2	9.4
oral exposure by hand-to-mouth contact when getting access to the used pipette	child	25	56
oral exposure by hand-to-mouth contact when stroking/handling the treated animal on the day of treatment	adult	833	2000
oral exposure by hand-to-mouth contact when stroking/handling the treated animal on the day of treatment	child	151	309
oral exposure by hand-to-mouth contact when stroking/handling throughout day 1-28 after treatment of the animal	adult	340	333
oral exposure by hand-to-mouth contact when stroking/ throughout day 1-28 after treatment of the animal	child	51	50

Risk management and risk communication

The following warning sentences are included in section 4.5 of the SPC:

- Do not eat, drink or smoke while handling the veterinary medicinal product
- The sachet is child-resistant. Keep the product in the sachet until use, in order to prevent children from getting direct access to the product. Keep the used pipette out of reach and sight of children. Used pipettes should be disposed of immediately.
- Wash hands immediately after use.
- This product contains indoxacarb and permethrin. People with known hypersensitivity to indoxacarb and/or permethrin should avoid contact with this product.
- As the veterinary medicinal product may cause moderate eye irritation, avoid contact with eyes. If this occurs, rinse slowly and gently with water.

The proposed risk mitigation measures are sufficient to reduce the risk of dermal exposure in adults to an acceptable level.

The risk of oral exposure in children by hand-to-mouth contact when stroking/ throughout day 1-28 after treatment of the animal is considered acceptable because the exposure is very worst case.

The risk of eye irritation is sufficiently minimised with the proposed risk mitigation measures.

The sachet is child resistant; therefore the risk of child exposure is sufficiently reduced.

Environmental risk assessment

A phase I environmental risk assessment was conducted, which showed that the assessment can stop (at question 3 of the decision tree), because the product is not intended to be used in any food producing species. A Phase II assessment is therefore not necessary.

Considering the nature of the product the impact on the environment was still further considered. The product will dry fast and the active ingredients will stick to the coat. The probability of release from the coat when a dog swims in water is very low, based on (1) the high log Kow values and (2) the fact that the product remains active after shampooing.

In view of the data provided, the following wording in the SPC is considered appropriate:

In part 4.5:

"The veterinary medicinal product remains effective when treated animals are exposed to sunlight or immersed in water (e.g. swimming, bathing). However, dogs should not be allowed to swim or be shampooed within 48 hours after treatment. In case of frequent shampooing, the duration of activity may be reduced."

And in part 6.6:

"Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

Activyl Tick Plus should not be allowed to enter surface waters as indoxacarb and permethrin may have harmful effects on aquatic organisms."

Overall conclusions on the safety documentation

The toxicological profile of indoxacarb has been demonstrated by data submitted for the application made for Activyl.
Adequate safety has been demonstrated by tolerance studies carried out with indoxacarb as Activyl in the dog.

For permethrin literature and studies on the fixed combination have been submitted.
For further information on the safety of permethrin for the dog, the applicant refers to data on Exspot (Pulvex), an authorised spot on formulation that has been used on dogs for decades.
The number of reported adverse events is very low and the use of permethrin can be considered to have an acceptable level of safety. The use of permethrin is considered well established.

The absence of pharmaceutical/pharmacodynamic interaction of indoxacarb and permethrin has been demonstrated. It is concluded that the combination is unlikely to change the safety of both single substances.

The product is not expected to pose a risk for the user when used as recommended and appropriate warnings are included in the SPC.

The product is not expected to pose a risk for the environment when used as recommended and appropriate warnings are included in the SPC.

Part 4 – Efficacy

Indoxacarb

Indoxacarb is a synthetic insecticide that acts by blocking the sodium channel in neurons, a mode of action first identified in pyrazolines. Indoxacarb belongs to the oxadiazine class of insecticides (oxadiazine analogue of the pyrazoline ring system). Its original use was for the control of pest insects on a wide variety of plants, including vegetables, fruit trees, cotton, and row crops. Because of its use in agriculture, extensive information is available on the toxicity profile of this molecule, as well as its safety for mammals and the environment.

In order to be effective indoxacarb has to be metabolised. In the insect indoxacarb is converted to a more toxic substance IN-JT333. Indoxacarb and IN-JT333 possess different profiles in their potency in blocking sodium channels and the reversibility of the blocking effects in mammalian neurons, the metabolite being the most effective one.

Indoxacarb is a chiral molecule, the S-enantiomer (>99% S-isomer; DPX-KN128) is the insecticidal active substance; the R-enantiomer has no such activity. Both enantiomers are similar with respect to the toxic effects in the target animals.

The bioactivated metabolite of indoxacarb induces a hyperpolarisation of the membrane potential associated with an increase in input resistance and a reduction in action potential amplitude. It blocks the inward sodium current amplitude of the neurone without modification of either inactivation or activation kinetics, which is the case for pyrethoids.

The binding affinity of sodium channels, for indoxacarb and for its insecticidally active metabolite, is different in insects and mammals.

The voltage-dependent sodium channel blocking action of pyrazolines in mammals is known. This mechanism closely mirrors the action of therapeutic sodium chaimel blockers such as local anaesthetics.

Permethrin

Permethrin is a Type I synthetic pyrethroid. Type I pyrethroids can act as acaricides and insecticides, with repellent efficacy. The spectrum of activity includes flies, fleas, ticks, lice and mites.

Pyrethroids primarly affect voltage-gated sodium channels in vertebrates and non-vertebrates.

Insect sodium channels are up to 1000 times more sensitive to pyrethroids than mammalian sodium channels. Furthermore, mammalian sodium channels recover more rapidly and detoxification rate in mammals is higher.

Pyrethroids have a negative temperature effect, meaning that toxicity increases at lower temperatures.

Permethrin is a racemic mixture (R-cis/trans and S-cis/trans), with differences in effects and toxicity. The 1R cis isomer is the neurotoxic and most active one. The 1S trans isomer is inactive and not toxic to mammals.

Permethrin has a widespread use in agriculture, industry, public health, veterinary medicine and domestic environment for decades.

Permethrin posesses repellent and lethal efficacy agianst ticks. Permethrin has been marketed as Exspot (also known as Pulvex spot) worldwide as a veterinary medicinal product for the dog, including in the EU for more than 10 years.

Permethrin is or has also been marketed by many other companies for the same purpose.

The topical use of permethrin for the control of tick infestations in dogs is considered well-established.

The fixed combination product Activyl Tick Plus

As both substances act on nerve sodium channel function, studies were carried out to investigate possible interaction between indoxacarb and permethrin. Indoxacarb blocks the ion transport through the sodium channels. Permethrin leads to prolongation of opening of these channels.

Although nerve sodium channels are the target for both substances, it was concluded that they do not share the same mode of action. Their pharmacodynamic effects do not interact as indoxacarb and permethrin seem to have different binding sites.

The justification of the recommended treatment dose for Activyl Tick Plus is based on the dose of Activyl, containing indoxacarb only, and on the dose of Exspot (Pulvex), containing permethrin (40:60) only.

Development of resistance

Both indoxacarb and permethrin exert their activity via the neuronal sodium channels. However, binding sites are different. Therefore, cross resistance is not likely to occur.

Routes for uptake are different, with permethrin via contact through the cuticle and indoxacarb via oral uptake. These complementary routes are expected to reinforce the insecticidal efficacy, further preventing the potential development of resistance.

Resistance in fleas has been reported for permethrin. Most reports are anecdotal and data describing the degree and stability of the perceived resistance are very limited. As other active substances with different mode of actions have become available, the use of permethrin for flea control has reduced.

Although permethrin has been used for many years to control tick infestations, only a few reports on resistance mainly concerning cattle, not the dog, have been published.

Pharmacokinetics

For pharmacokinetic information on the single substances, the applicant refers to the data on Activyl for the indoxacarb and to literature for permethrin.

Furthermore, the applicant has submitted information on the absorption, distribution metabolism and excretion of indoxacarb and permethrin when applied to the dog as a single topical administration using the proposed final formulation.

Dose determination/justification

No new dose determination studies were carried out. The dose for indoxacarb was based on that of Activyl and the dose for permethrin was based on that of Exspot (Pulvex). Due to formulation requirements concentrations of both active substances differ from those of the original formulations for the mono-substance products.

To confirm the efficacy of the recommended minimum dose of 15 mg indoxacarb/kg bw, and 48 mg/kg permethrin mg/kg bw, 12 dose-confirmation studies have been carried out.

In these studies, therapeutic and preventive efficacy in dogs were studied as well as repellence against ticks, using experimental infestation models with fleas (*Ctenocephalides felis*) and various tick species.

Results indicated a therapeutic efficacy against flea infestations, with a subsequent preventive effect over the recommended treatment interval.

For existing tick infestations, an immediate efficacy claim could not be accepted: a 3 day period after administration was needed to reduce tick counts by >90%. Based on the data presented, it was demonstrated that the product has persistent acaricidal efficacy for up to 5 weeks against *Ixodes ricinus* and up to 3 weeks against *Rhipicephalus sanguineus*; however, the data presented were considered inadequate to support a persistent efficacy claim against *Dermacentor reticulatus*.

The veterinary medicinal product remains effective after exposure to sunlight or water immersion (swimming, bathing). However, dogs should not be allowed to swim or be shampooed within 48 hours after treatment. In case of frequent shampooing, the duration of activity may be reduced.

Exposure of flea eggs to debris from treated animals reduced hatching > 95% for about 5 weeks.

The CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.2) indicates that for the calculation of efficacy (against fleas and/or ticks), 'arithmetic means are usually acceptable for the calculation. If geometric means are used, the transformation must be justified and the arithmetic means also recorded.' It is considered that the applicant has not provided adequate justification for the use of geometric means in determining the efficacy of the product. Therefore, efficacy (the accepted indication) was determined based upon arithmetic mean data and not geometric mean data.

Target animal tolerance

The safety of the fixed combination product was investigated by 5 tolerance studies, carried out on the dog and using the final formulation of the product.

- Three studies concerned a topical application of the product at the recommended dose and a 3 and 5 times overdose, given at 2 week intervals for a period of 10 weeks and at 4 week intervals for a period of 6 months.
- One study concerned the oral safety of the product at 0.1, 0.3, 0.5, 0.7 and 1x the recommended treatment dose as a single administration and
- One study investigated reproductive safety of the product when administered at 3 x Recommended Therapeutic Dose (RTD) at 28 day intervals.

Results indicate that the recommended dose can safely be used in dogs starting at the age of 8 weeks and when used at 4 week intervals as recommended for a period of 6 months. As can be expected for topical solutions, cosmetic effects on the application spot are visible and some dogs may show a slight dermal irritation. Such effects disappear without treatment.
Oral administration of the fixed combination product did not result in adverse effects.

In the reproductive safety study at 3x overdose, a change in the live pup ratio was observed. Whether this was treatment related remains unclear, however a treatment related effect could not be fully excluded. Other adverse effects were not noted. Reproductive safety has not been investigated at the recommended dose. In the light of these findings, the SPC 4.7 includes the following precaution:

"Laboratory animal studies (rats, mice and rabbits) with indoxacarb and permethrin have not produced any evidence of a teratogenic, foetotoxic or materno toxic effects. However, a reproductive toxicity study conducted in the dog at three times the recommended therapeutic dose did reveal a significant reduction in the live pup ratio; the clinical significance of this latter finding is unknown as no studies were carried out in dogs using the recommended therapeutic dose. Therefore the use of the product in

pregnant and lactating animals or animals intended for breeding should be based on a benefit/risk assessment by a veterinarian."

Field trials

The applicant submitted the data of 3 field studies, 2 of them carried out in Australia and 1 carried out in the EU. In all studies the final formulation of the fixed combination product was used and administration was according to the proposed dose, every 4 weeks and for a period of 84 days.

The studies carried out in Australia concerned flea infestations only. Efficacy was high (95-100% reductions) and a rapid reduction of flea populations was observed at households included in the study. No adverse reactions were observed.

The EU-study involved 6 veterinary practices (2 in Spain, 2 in France and 2 in Germany) including a total of 148 dogs treated with the indoxacarb/permethrin fixed combination and a total of 46 dogs treated with a reference product containing fipronil.

The study covered an 84-days period with 7 visits at 14 -day intervals, at which treatment effects were evaluated. At inclusion (1st visit) tick/flea counts were made and the animal was treated. Further visits were scheduled every 2 weeks at which tick/flea counts were made and animals were examined for possible skin lesions. Ticks found on the animal were removed and identified.
Animals were treated according to the (proposed) label instruction which was every 4 weeks for both products.

Both treatments reduced flea and tick numbers to almost zero during the whole of the study period. The predominant tick species found was *Ixodes* spp.

The number of animals suffering from flea allergy dermatitis (FAD) was very low and no conclusion on the effect of treatment could be made.

Adverse events were observed in the indoxacarb/permethrin-treated group and concerned skin lesions of which 8/148 were considered possibly related to treatment.

Overall conclusion on efficacy

It is concluded that the safety of the fixed combination product has been demonstrated for the dog, when used as recommended.

Data support a treatment and prevention claim for fleas and a persistent efficacy claim for ticks (*Ixodes ricinus* and *Rhipicephalus sanguineus*) for the fixed combination of indoxacarb and permethrin. The following indication was considered acceptable:"*Treatment of flea infestations (Ctenocephalides felis); the product has persistent insecticidal efficacy for up to 4 weeks against Ctenocephalides felis.*

The product has persistent acaricidal efficacy for up to 5 weeks against Ixodes ricinus and up to 3 weeks against Rhipicephalus sanguineus. If ticks of these species are present when the product is applied, all the ticks may not be killed within the first 48 hours but they may be killed within a week.

The veterinary medicinal product can be used as part of a treatment strategy for flea allergy dermatitis (FAD).

Developing stages of fleas in the pet's immediate surroundings are killed following contact with Activyl Tick Plus treated pets."

Part 5 – Benefit risk assessment

Introduction

Activyl Tick Plus is a spot-on solution for the treatment and prevention of fleas and ticks in dogs and can be used as part of a treatment strategy for flea allergy dermatitis. The product contains two active substances, indoxacarb; an ectoparasiticide belonging to the oxadiazine chemical family, and has a history of use in plant protection and permethrin; a Type I synthetic pyrethoid which acts as an acaricide and insecticide, with repellent properties.

Benefit assessment

Direct therapeutic benefits

Permethrin has both insecticidal and acaricidal efficacy.

With respect to ectoparasites on dogs permethrin is active against fleas and ticks.

Indoxacarb is effective in controlling flea infestations and also preventing flea larval development in the surroundings of the treated animal.

The fixed combination of indoxacarb and permethrin is able to eliminate existing flea infestations. It has a persistent efficacy controlling and preventing flea and tick infestation for up to 3-4 weeks after administration. However, the product is not sufficiently effective against an existing tick burden.

Indirect or additional benefits

Indoxacarb is an active substance for the control of flea infestations.

The fixed combination reduces the need for using 2 different products against flea and tick infestations.

Five different presentations are supplied to facilitate flexibility in dosing for small to large dog sizes at the recommended treatment dose.

Risk assessment

Both indoxacarb and permethrin are of low toxicity to mammals and data for this product have shown no systemic adverse reactions in target animals. Local reactions at the application site have been observed.

The product is not expected to pose a risk for the user or the environment when used as recommended and taking into account the risk mitigation SPC warnings include in sections 4.5 and 6.6.

To protect children from exposure to the content of a pipette, the applicant provided a child-resistant packaging.

Evaluation of the benefit risk balance

It can be concluded that the product appears to be effective and safe for target animals and for the users. The benefit risk balance is deemed positive.

Conclusion

The available data adequately support the claimed indication. No unacceptable risks are identified. Consequently, the benefit risk balance is positive.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Directive 2001/82/EC as amended.