10 September 2015
EMA/605662/2015
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Simparica (EMEA/V/C/003991/0000)

International non-proprietary name: sarolaner

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Introduction

On 24 November 2014, the applicant Zoetis Belgium SA submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for Simparica, through the centralised procedure falling within the Article 3(2)(a) of Regulation (EC) No. 726/2004 (new active substance).

The eligibility to the centralised procedure was agreed upon by the CVMP on 10 April 2014 as Simparica contains a new active substance, sarolaner, which was not authorised as a veterinary medicinal product in the Community on the date of entry into force of the Regulation.

The rapporteur appointed was D. Murphy and co-rapporteur P. Hekman.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

Simparica chewable tablets contain sarolaner as active substance, an ectoparasiticide belonging to the isoxazoline group, which is active against ticks, mites and fleas. The product is presented in six strengths (5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 120 mg) packaged in blister packs, within cardboard cartons containing either 1, 3 or 6 tablets. The route of administration is oral use. The product is intended to be used in dogs for the treatment of flea, tick and mite infestations.

On 10 September 2015, the CVMP adopted an opinion and CVMP assessment report.

On 6 November 2015, the European Commission adopted a Commission Decision granting the marketing authorisation for Simparica.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The active substance (sarolaner) is manufactured outside the EEA. A Qualified Person (QP) declaration is provided by the QP at the EU batch release site. The declaration is issued on behalf of all sites involved in the manufacture of the dosage form and issued on foot of an audit of the active substance manufacturing site in May 2014.

The finished product is manufactured and packed outside the EEA. Batch release for the EU will be carried out by Zoetis Belgium SA.

Manufacture of the product involves manufacture of an intermediate product containing the active substance which is then combined with tableting excipients to produce the finished product. Evidence that all sites are appropriately authorised for the operations conducted for such veterinary medicinal products has been included in the dossier.

No concerns have been raised during the assessment that would give rise to any manufacturing site inspection prior to authorisation.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system is considered in line with legal requirements.

The GMP status and manufacturing authorisation for the active substance and dosage form manufacturing sites, respectively, have been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

Simparica chewable tablets are available as 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 120 mg strengths. The tablets are mottled brown coloured and square-shaped (with rounded edges), with an identification number embossed on one side of the tablet referring to its strength (for example, “5”).

In addition to the active substance the chewable tablets contain the following excipients: hydroxypropyl methyl cellulose acetate succinate MG (HPMC-AS MG), spray dried pork liver powder, hydrolysed vegetable protein, maize starch, lactose monohydrate, confectioner’s sugar, wheat germ, calcium hydrogen phosphate anhydrous, glucose liquid (81.5% solids), gelatin Type A, sodium starch glycolate, silica colloidal anhydrous and magnesium stearate. With the exception of the HPMC-AS MG polymer, all of the excipients are commonly used in veterinary medicinal products.

Container

The primary packaging is aluminium/aluminium (cold formed) blisters, and the tablets are packaged in the blisters in configurations of 1, 3 or 6 tablets per blister strip.

The product contact layer is polyvinyl chloride (PVC) which complies with EU Regulation 10/2011 on plastic materials and articles intended to come into contact with food, and also with the requirements of the European Pharmacopoeia (Ph. Eur.) monograph 3.1.11 (Materials based on non-plasticised poly(vinyl chloride) for containers for dry dosage forms for oral administration).

Secondary packaging consists of a cardboard carton (each containing a package leaflet).

Development pharmaceutics

A comprehensive report on development pharmaceutics is presented describing the development and selection of the intermediate product, selection of excipients and manufacturing process development.

The development of the intermediate product is well described in terms of method selection, excipients selection, drug loading and critical parameters. In the formulation optimisation studies the palatable base granules (PBG) component was varied as a single entity. The PBG is a flavouring agent/filler used in other chewable tablets already authorised in veterinary medicinal products in the EU. The level of inclusion is based on previous experience and was evaluated based on palatability and dissolution studies.

The final formulation was used for most of the clinical studies. An early development (prototype) formulation was used in some early pre-clinical and clinical studies but the differences between it and the final formulation are not expected to have any impact on the outcome of these trials. This is supported by a comparative pharmacokinetic study in which the PK profiles for both the prototype and the final formulation were shown to be broadly similar.

Development of the manufacturing process of the intermediate product is well described and proven acceptable ranges for the critical quality attributes have been established. Development of the manufacturing process of the chewable tablets is also well described. Quality criteria were evaluated as appropriate during process development.

The choice of the materials incorporated in the formulation is discussed and justified.

Method of manufacture

A common powder blend is used to manufacture all the chewable tablet strengths.

The chewable tablets are manufactured by dry granulation, combining the intermediate product (containing the active substance sarolaner), the palatable base granules and the remaining tableting excipients. The final (common) blend is then compressed into tablets of the required weight and packaged.

The description of the manufacturing processes for the intermediate product the palatable base granules and the chewable tablets contain sufficient details and include appropriate in-process controls.

The manufacture of the intermediate product is not a standard manufacturing process as defined in the CVMP guideline on process validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/70278/2012-Rev.1) and process validation data for this process is therefore provided for three batches.

A process validation scheme is provided for the validation of the chewable tablets.

A brief summary of process validation for three batches of the palatable base granules is provided. Results of in-process controls are not provided. Batch data are provided for the three batches. The data provided is limited, nevertheless it is accepted that the process has been validated and the palatable base granules are already used in several authorised products.

Control of starting materials

Active substance

The active substance, sarolaner, is a member of the isoxazoline class of parasiticides, and is a poorly soluble drug. Sarolaner is supplied by a single source and is manufactured in a four step synthetic process using three starting materials. The active substance has one chiral centre at the 5 position and the manufacturing process routinely produces the same isomer. The other isomer is identified as an impurity and controlled on the specification. The structure is fully elucidated.

One of the starting materials, is considered to be quite complex, however, acceptable justification has been provided for its designation as a starting material, coupled with a detailed characterisation of the starting material and its potential impurities, along with a specification that is deemed to be suitable for its control. As such, the starting material is considered to be acceptable and batch data is provided for active substance manufactured from starting material from each of the different proposed suppliers.

The level of detail provided for the active substance manufacturing process is sufficient. Specific detail of the manufacturing process is included in the dossier, including in-process controls for optional steps and specific detail on reprocessing and intermediate specifications.

The applicant is recommended to amend the manufacturing process as soon as commercial scale validation has been completed with commercial batches manufactured using the new manufacturing process proposed.

The in-house specification for the active substance is acceptable. Test methods are well described and are validated in accordance with VICH GL2 Validation of analytical procedures: Methodology. Batch analysis data is provided for 9 batches (laboratory and pilot scale) of the active substance manufactured throughout the development of the synthetic process. Batch analysis data on full-scale batches manufactured according to the new process proposed have been provided.

Stability studies were initiated on three batches of the active substance, manufactured at an active substance development site, at approximately one-third of the production scale. 12 month data at 25 °C/60% RH and 30 ^{o}C/75% RH and 6 months data at 40 ^{o}C/75% RH are currently available. In addition, the 2 batches manufactured at the active substance manufacturing site were also placed on stability. 12 month data at 25 °C/60% RH and 30 ^{o}C/75% RH and 6 months data at 40 ^{o}C/75% RH are currently available for one of these batches and 2 month data at 40 ^{o}C/75% RH is available for the second batch. Finally, 18 month supporting stability data at 25 °C/60% RH has been provided on a batch of the active substance manufactured at a development site.

The samples were packaged in a container-closure system that simulates that used for the bulk active substance (i.e. in double LDPE bags in either a HDPE or fibreboard drum). All results were within the proposed specifications with only minor decreasing trends or overall decreases in assay noted for some of the batches. Therefore, it is considered that the proposed re-test period of two years with no specific storage precautions is supported by the stability data provided.

The applicant is recommended to place the first 3 production batches on stability.

Excipients

Many of the excipients used in the formulation are monographed in the Ph. Eur. and comply with their respective monographs (lactose monohydrate, sodium starch glycolate Type A, silica colloidal anhydrous, magnesium stearate, maize starch, lactose monohydrate, calcium hydrogen phosphate anhydrous, glucose liquid, gelatin Type A).

Some other excipients comply with USP monographs (hypromellose acetate succinate MG, confectioner's sugar). For the hypromellose acetate succinate MG excipient the "M'' designation relates to medium grade acetyl to succinoyl ratio and the 'G' designation to a granular grade.

Some excipients are not monographed and comply with in-house monographs (spray dried pork liver powder, hydrolysed vegetable protein, wheat germ).

In addition to the specifications for the excipients a specification is provided for the palatable base granules.

All the specifications and certificates of analysis provided comply with the relevant requirements.

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

The only materials of animal origin used in the manufacture of the finished product are lactose monohydrate, spray dried pork liver powder and gelatin Type A.

The spray dried pork liver powder is sourced from porcine liver and the gelatin is sourced from porcine skin. Pigs are however not TSE-relevant animal species within the meaning of the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01-rev. 3).

A declaration is provided that the lactose is derived from milk sourced from healthy cows, fit for human consumption and that the calf rennet used for production of the raw material whey meets the requirements of the TSE Note for Guidance.

The product is therefore out of scope of the relevant Ph. Eur. monograph and the Note for guidance.

A declaration of compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01-rev. 3) has been provided with respect to the excipients and the finished product.

Control tests during production

A specification for the intermediate product is provided. Further information on an analytical method for the intermediate product should be provided post-authorisation. The remaining analytical methods and their validation are in accordance with VICH GL2 Validation of analytical procedures: Methodology and have been well described. The critical steps in the manufacturing processes of the intermediate product and of the chewable tablets are justified by data provided. The intermediate product is packaged in two LDPE bags with desiccant placed between the bags and then stored in an HDPE drum or equivalent secondary container.

Control tests on the finished product

Specifications for the chewable tablets are proposed, for both release and end of shelf life, which include tests for description, identification, water content, content uniformity, assay, degradation products, dissolution and microbiological quality. The specifications are in accordance with VICH GL39 Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances and the proposed limits are acceptable to control the quality of the finished product and includes relevant test parameters and limits.

Analytical methods are well described and have been validated in accordance with VICH GL2 Validation of analytical procedures: Methodology.

Batch data is provided for several batches of each tablet strength, including batches used in the clinical studies and VICH stability batches. All results are within specification with low levels of impurities or no impurities detected.

Stability

Intermediate product

Stability studies were initiated on three batches of the intermediate, manufactured at the proposed commercial manufacturing site at approximately half of the production scale. 9 month data at 25 °C/60% RH and 6 month data at 40 °C/75% RH were provided. Supporting stability data has been provided on three pilot scale batches of the intermediate manufactured at a development site. 12 month data at 25 °C/60% RH and 6 month data at 40 °C/75% RH are provided for these batches. Batches were packaged in the commercial pack (double low density polyethylene (LDPE) bags inside high density polyethylene (HDPE) containers along with desiccant).

All results were within the proposed specifications but with some overall decreases in assay noted for some of the batches. Levels of impurities did not change over the course of the stability studies. A slight trend in increasing water content was observed under both real-time and accelerated conditions for the primary stability batches. Based on both the primary and supporting stability data the proposed expiration date for this intermediate is considered acceptable.

Finished product

Primary stability data are presented for three batches of each tablet strength manufactured at the proposed dosage form manufacturing site and packaged in the intended commercial Alu/Alu blister. 6 month data at 25 °C/60% RH, 12 months at 30 °C/65% RH and 9 months at 40 °C/75% RH were provided.

Supporting stability data are also presented for five batches manufactured at a development site. These batches are packaged in either HDPE bottles or Alu/Alu blisters with a slightly thicker foil layer to that proposed. 18 month data is available at 30 °C/65% RH and 6 month data at 25 °C/60% RH and 40 °C/75% RH.

Results for appearance, assay, water, degradation products, dissolution, hardness, friability and microbiological quality are reported for the primary stability batches. The parameters hardness and friability are not controlled by the shelf life specification but are reported for information purposes for these stability studies.

The data presented demonstrates that the stability of the tablets is good. The results reported are within specification across all batches and storage conditions. In the supporting stability studies all results for the product packaged in blisters are within specification across all batches and storage conditions. The data from both the primary and supporting stability studies indicate that the product is stable, nevertheless it is accepted that the limit for assay over the shelf life is reasonable to allow for inter- and intra- batch fluctuations. This will not adversely affect the efficacy of the product.

On the basis of satisfactory real time stability data to 12 months and satisfactory accelerated stability data to 6 months and 9 months, the proposed 2 year shelf life by extrapolation is considered to be acceptable for the finished product as packaged for sale. In accordance with the annex to EMEA/CVMP/453/01, the start of shelf life for the product is the date of manufacture of the intermediate product as this is the date that the first step is performed involving combining the active ingredient with other ingredients.

In accordance with EMEA/CVMP/422/99 (Guideline on declaration of storage conditions), no specific temperature storage precautions are required for the product. A VICH GL5 compliant photostability study demonstrates that no special storage conditions are required with respect to photosensitivity.

Overall conclusions on quality

The product is manufactured by dry granulation using excipients that are widely used in tablet formulations, with the exception of the polymer HPMC-AS MG. The composition of the product has been justified.

Extensive formulation development is described in the dossier from the active substance's physicochemical properties, development of the intermediate product, to excipient selection and optimisation and manufacturing process optimisation.

Development of each of the various manufacturing processes is well described and process optimisation has been undertaken at development scale. The level of detail provided with respect to the commercial manufacturing processes is acceptable and appropriate in-process controls are described. A process validation report for the non-standard method of manufacture of the intermediate product is provided.

The manufacturing process for the active substance is a four step chemical synthesis. Three starting materials are used in the process. Although one of the starting materials is considered to be quite complex, acceptable justification has been provided by the applicant for its choice as a starting material, along with a detailed characterisation of the starting material and its potential impurities, and a specification that is deemed to be suitable for its control. As such, this starting material is considered to be acceptable. Details of the manufacturing process for the active substance and its control are adequately described in the dossier and appropriate in-process controls are described. It is recommended that the manufacturing process is amended as soon as commercial scale validation has been completed with commercial batches manufactured using the new manufacturing process proposed. Stability data is provided for pilot scale batches to support a 24 month re-test period for the active substance and stability data from the first 3 production batches with the new manufacturing process is recommended to be provided when available.

A specification for the intermediate product is provided.

The specifications proposed for the chewable tablets at release and at the end of shelf life are in line with current guidance and are appropriate to control the quality of the finished product. The limit for assay in the shelf life specification is justified. Analytical methods and their validation are adequately described. The relevant EU and VICH guidance and Ph. Eur. requirements are taken into account.

Suitable stability studies have been carried out, under both long term and accelerated conditions, according to current VICH guidelines and these demonstrate the product to be stable with no adverse trends in any of the parameters investigated. The stability data provided support a shelf life of 2 years without any special storage precautions.

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate the consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant is recommended to provide further information post-authorisation on the manufacture of the active substance and its stability, and of an analytical method for the intermediate product.

Part 3 – Safety

The active substance, sarolaner, a systemically acting ectoparasiticide, is a new active substance not previously authorised in a veterinary medicinal product in the EU. A full safety file in accordance with

Article 12(3)(j) has been provided.

Safety documentation

Pharmacodynamics

See Part 4.

Pharmacokinetics

See Part 4.

Toxicological studies

Single dose toxicity

To characterise the acute toxic potential of sarolaner, single-dose studies using the oral and dermal routes of administration were conducted in rats (both were GLP studies conducted in accordance with the relevant OECD guideline). In addition, a non-GLP safety study in dogs administered single oral doses given at 7-day intervals is presented.

In the acute oral study in rats, the acute oral LD_{50} was estimated to be 783 mg/kg (95% confidence interval of 550–2000 mg/kg). Adverse effects included body tremors. In the dog, serious adverse effects occurred at an oral dose of 62.5 mg/kg (vomiting, stiff jerky movements, convulsions). While no significant adverse reactions were observed at single oral doses ≤25 mg/kg, only single animals were tested with doses ≤25 mg/kg.

In the acute dermal toxicity study, a dose of 2020 mg/kg did not result in any clinical signs of toxicity or signs of dermal irritation. No mortality occurred during the study. The dermal LD_{50}, as indicated by the data, was determined to be >2020 mg/kg.

These studies provide useful information on the acute toxicity of sarolaner via the possible routes of exposure that the user/animal owner may encounter. However, when considering acute toxic potential relating to oral exposure, consideration must also be given to the findings of the repeat-dose studies in the dog, where adverse effects (neurological) were detected on the day of dosing. See below.

Repeat dose toxicity

The toxicity of sarolaner was profiled in oral (by gavage) repeat-dose 30- and 90-day studies in rats (both were GLP studies conducted in compliance with the relevant OECD guideline) as well as in target animal safety (TAS) studies in dogs.

Studies in rats:

Sarolaner was administered orally to Crl:WI(Han) rats at dosage levels of 0 (vehicle), 0.223, 2.233, and 22.33 mg/kg/day for 30 consecutive days. Test article-related lower body weight gains or body weight losses and corresponding lower food consumption were noted in the 22.33 mg/kg/day group males and females from Study Day (SD) 0 to 7. Females showed partial recovery from the body weight effects following the first week of the dosing period. Clinical observations of thin body condition and dermal atonia correlated with the body weight effects were noted in a single female on SDs 7 and/or 8. In males,

complete recovery from the body weight and food consumption effects was noted following the first week of the dosing period. No test article-related clinical observations were noted in the males. Changes in clinical pathology parameters were slight. Test article-related gross enlargement of the adrenal glands at 22.33 mg/kg/day in both genders was related to higher adrenal gland weights and microscopic hypertrophy of zona fasciculata cells of the adrenal cortex. In this study, there is no evidence of stress being a cause of the adrenocortical cell hypertrophy (i.e., no stress leukogram and no thymic atrophy). Based on the results of this study, the applicant proposes a no-observed-adverse-effect level (NOAEL) of 2.233 mg/kg/day (actual dosage level). However, at this dose, effects on the liver were observed (dose dependent vacuolation in females accompanied by decreased triglyceride levels in blood). Moreover, vacuolation in the adrenal gland was observed in males and adrenal gland weights were increased in females. Also (dose dependent) histopathological changes were observed in the ovary. These effects are consistent with those observed in the 90 day study and considered adverse reactions. Therefore, a NOAEL for this study of 0.233 mg/kg bw would appear more appropriate. At this dose, the vacuolation in liver and ovary hypertrophy is considered mild and non-adverse.

Sarolaner was administered orally to Crl:WI(Han) rats at dosage levels of 0 (vehicle), 0.025, 0.25, 2.5, and 25 mg/kg/day for 90 consecutive days. Test article-related lower body weight gains and corresponding lower food consumption were noted in the 25 mg/kg/day group males and females from Week 0 to 1. Although the lower food consumption persisted through the end of the study, the animals showed complete (males) or partial (females) recovery from the body weight effects following the first week of the dosing period.

Changes in clinical pathology parameters were slight and were considered non-adverse.

Test article-related pale adrenal glands were noted in the 25 mg/kg/day group males and females and correlated with higher adrenal gland weights and hypertrophy or vacuolation of the adrenal cortex. In addition, vacuolation of interstitial cells of the ovary was noted in the 0.25, 2.5, and 25 mg/kg/day group females and correlated with higher ovary weights in females administered 25 mg/kg/day of the test article, but there was no evidence that the changes in the adrenal cortex or ovary affected organ function and therefore were not considered to be adverse. Based on the results of this study, oral administration of sarolaner to Crl:WI(Han) rats for 90 or 91 consecutive days resulted in a NOAEL of 25 mg/kg/day. The CVMP did not accept the proposed NOAEL given that an effect on body weight was noted at 25 mg/kg/day and, for females, only a partial recovery of this effect was achieved over the remainder of the study. In addition, at 25 mg/kg/day, effects on food consumption persisted throughout to the end of the study. Furthermore, treatment-related histopathological (dose-dependent) changes in the ovary were noted at lower doses. Therefore, a NOAEL for this study of 0.25 mg/kg bw would appear more appropriate. At this dose vacuolation in the ovary is considered mild and non-adverse.

Studies in dogs:

The target animal safety for sarolaner has been investigated in several studies including the pivotal target animal safety study, a GLP margin of safety study in dogs; as well as an exploratory tolerance study in puppies, an exploratory margin of safety study in dogs (non-GLP) and a pilot escalating dose tolerance study in adult dogs. In addition, a study was conducted to evaluate the safety of sarolaner when administered to avermectin-sensitive Collie dogs.

In the pivotal margin of safety study, neurological effects were noted at doses of 20 mg/kg (convulsions, tremors and ataxia) and 12 mg/kg (tremors, ataxia). Signs appeared to occur primarily in the first 24 hours after dosing and resolved without treatment. In this study, no effects on the nervous system were observed in any animal at 4 mg/kg. Apart from the neurological effects, the CVMP accepted that the target animal safety studies do not result in other findings of toxicological concern.

See Part 4, Target Animal Tolerance, for further discussion of this point.

Tolerance in the target species of animal

See Part 4.

Reproductive toxicity

Studies to evaluate the effects of sarolaner on reproduction were not conducted. Given that this application relates to a product intended for non-food animals, the absence of specific reproductive toxicity studies can be accepted. In the absence of reproductive toxicity studies, the SPC includes a statement that the safety of the product has not been established during pregnancy and lactation or in animals intended for breeding.

The definitive developmental toxicity studies in rats and rabbits were conducted in accordance with GLP and OECD 414. These studies were adequate to evaluate maternal and embryo/foetal toxicity and teratogenic potential during the period of organogenesis. The NOAEL for maternal toxicity and embryo/foetal development was determined to be 3.2 mg/kg/day when administered orally to Crl:WI(Han) female rats and 3.0 mg/kg/day when administered orally to time-mated New Zealand White rabbits.

Mutagenicity / genotoxicity

The mutagenic potential for sarolaner was adequately assessed in a standard battery of genetic toxicology assays recommended in VICH GL23. All studies were GLP and were conducted in accordance with the relevant OECD guidance.

- Sarolaner did not induce mutations either directly or with metabolic activation in *Salmonella typhimurium* or *Escherichia coli* strains at any dose tested in the Ames assays.
- Sarolaner was negative for inducing structural and numerical (polyploidy-inducing endoreduplication) chromosome aberrations in human peripheral lymphocytes in the in vitro chromosome aberration assay.
- Sarolaner was negative in the in vivo micronucleus assay in male and female rats.

Based on the study results, sarolaner is not considered to be of mutagenic or genotoxic concern.

Carcinogenicity

Carcinogenicity studies were not conducted with sarolaner. The absence of carcinogenicity studies is acceptable on the basis that:

1. the test article was not mutagenic or genotoxic,
2. there were no proliferative changes in the 90-day oral rat toxicity study, and
3. there were no structural alerts for genotoxicity.

Studies of other effects

Sarolaner was minimally irritating in an ocular irritation study (GLP, OECD 405) (although the slight eye-irritation may be caused by applying the test compound as a solid into the eyes) and non-irritating in a dermal irritation study (GLP, OECD 404). Sarolaner is not considered a sensitizer based on results of a mouse local lymph node assay (GLP, OECD 429).

User safety

The applicant has presented a user safety assessment which has been conducted in accordance with the CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1). Sarolaner will be supplied as 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, and 120 mg flavoured chewable tablets dispensed individually in an aluminium foil/foil blister package with 1, 3 or 6 tablets per blister strip. The tablets are hard and are not divisible. It is expected that the tablet will be removed from the blister package by an adult pet owner and administered to the dog immediately. The tablet is palatable (see clinical field studies) and should be taken readily by most dogs with or without food.

For the adult user, the most relevant exposure route is dermal exposure at the time of product administration. While the applicant has not conducted a quantitative risk assessment for this exposure scenario, it is accepted that the risk of user exposure to the active ingredient is likely to be very low in view of the presentation and the tablet characteristics. Furthermore, while the adult pet owner/veterinarian could potentially be exposed to trace amounts of sarolaner through dermal exposure from handling the tablets and oral and ocular exposure from hand-to-mouth or hand-to-eye transfer, respectively, standard hygiene measures (washing hands after administering the product) will further minimise the potential for dermal, oral or ocular exposure. Accordingly, the risk to adults and veterinarians from dermal contact at the time of tablet administration is considered acceptable. The SPC and package leaflet include the following user warning: “Wash hands after handling the product.” This is considered acceptable.

For this product, the exposure scenario that represents the most significant risk is ingestion of a tablet by a child. For characterising the risk in this scenario, the most relevant toxicity study is the pivotal margin of safety study conducted in the dog. In this study, neurological effects were noted at doses of 20 mg/kg (convulsions, tremors and ataxia) and 12 mg/kg (tremors, ataxia). Signs appeared to occur primarily in the first 24 hours after dosing and resolved without treatment. In this study, no effects on the nervous system were observed in any animal at 4 mg/kg. Therefore, the applicant suggests that this is the minimum asymptomatic dose. This value can be accepted for the purpose of this assessment.

A 10 kg child accidently consuming the largest 120 mg tablet could result in an oral exposure of 12 mg/kg (for a 60 kg adult, the exposure would be 2 mg/kg). When comparing child exposure to the largest 120 mg tablet (12 mg/kg) to the proposed maximum asymptomatic single oral dose of 4 mg/kg administered to dogs, the margin of exposure (MOE) is 0.3. Notwithstanding the low MOE, this risk will be mitigated by the fact that the tablets are presented in robust blister packs and that the SPC and package leaflet carry the advice that “To prevent children from accessing the product, only one chewable tablet at a time should be removed from the blister pack and only when required.” and “The blister pack should then be returned into the carton immediately after use and the carton should be stored out of the sight and reach of children.” Furthermore, the label states “Keep out of the sight and reach of children”.

The blister lidding material is a commercially used peel-push lidding. The ease of opening of the blister packaging was investigated in two studies, a child study and a seniors study:

- In the child study (50 children; 30% of the participants were 42–44 months old, 40% were 45–48 months old, and 30% were 49–51 months old), each child was given two cards with six cavities in each card containing tablets. Access to nine or more cavities was considered a failure. No child managed to reach this threshold (interpreted as 100% effective).

- In the seniors study (100 senior adults; 25% of the participants were 50–54 years old, 25% were 55–59 years old, and 50% were 60–70 years old), each individual was given two packs. Only 3 of 100 participants failed to open the test packaging (interpreted as 97% effective).

Under the conditions of these tests, which are markedly in accordance with the European standard EN14375 for non-recloseable packaging material, the packaging meets the criteria for "child-resistant". Child-resistance has been satisfactorily demonstrated.

Regarding the overall conclusions on user safety, the risk to the user is considered acceptable noting in particular that:

- the pharmaceutical form (chewable tablet) limits the potential for the user to be exposed to the active substance when removing the product from the packaging and administering the tablet to the animal;

- the tablet is presented in child-resistant packaging; and,

- the product information includes a warning advising of the potential for adverse effects in case of accidental ingestion and specific instruction to remove tablets from the packaging only when required and to store out of the sight and reach of children.

The product does not pose an unacceptable risk to the user when used according to the SPC.

Environmental risk assessment

An environmental risk assessment (ERA) in accordance with VICH GL6 on environmental impact assessment for veterinary medicinal products - Phase I (CVMP/VICH/592/98-FINAL) and the CVMP guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1) was provided. This veterinary medicinal product is indicated for the individual treatment of non-food producing animals and will be administered orally to relatively small numbers of them.

Based on the data provided the ERA can stop at Phase I. Simparica chewable tablets are not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Sarolaner is a member of the isoxazoline class of parasiticides which acts by blocking the insect GABA gated chloride channels.

As the excipients are of low toxicity and/or present at low concentrations, the systemic and local toxicity of this product will be determined by its active substance, sarolaner. An adequate suite of toxicity studies on the active substance has been provided. In repeat-dose toxicity studies in rats, the target organs are the adrenal glands, liver and ovaries. In target animal safety studies, neurological signs were observed at overdose. Prenatal developmental toxicity studies have not shown any teratogenic effects, but studies of

the effects on reproduction were not provided. Sarolaner is not genotoxic and there is no need for carcinogenicity studies.

An adequate user safety assessment was provided. The exposure scenario that represents the most significant risk is ingestion of a tablet by a child. For this scenario, a margin of exposure (MOE) of 0.3 is calculated, based on the proposed no effect level on the nervous system in target animal safety studies. Notwithstanding the low MOE, it is accepted that this risk will be mitigated by the fact that the tablets are presented in robust blister packs and that the SPC and package leaflet include appropriate warnings. The CVMP concluded that the product does not pose an unacceptable risk to the user when used according to the SPC.

An adequate environmental risk assessment was provided. Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose a risk to the environment when used according to the SPC.

Residues documentation

Not applicable.

Part 4 – Efficacy

Pharmacodynamics

Sarolaner is an acaricide and insecticide belonging to the isoxazoline group. Isoxazolines act at the central nervous system or the neuromuscular junction of the insect, rather than directly on muscle fibres. The primary target of action of sarolaner in insects and acarines is the functional blockade of ligand-gated chloride channels (GABA-receptor and glutamate-receptors). By inhibiting these invertebrate chloride channels, sarolaner disrupts neuronal signalling and muscle regulation leading to death of insects (e.g. fleas) and acarines (e.g. ticks and mites).

Data provided by the applicant indicate that sarolaner is more potent at blocking insect/acarine receptors than mammalian receptors.

Development of resistance

Sarolaner is a new chemical entity. Since sarolaner and other members of the isoxazoline group have not been widely used yet in the general animal population, there has not been potential for development of resistance among the target parasites.

Pharmacokinetics

In rats, the plasma exposure of sarolaner (AUC and C_{max}) increased with increasing doses (0.025–25 mg/kg/day) and indicated some accumulation of sarolaner over the duration of the studies (29 and 89 days).

The pharmacokinetics of sarolaner in dogs were investigated in a series of laboratory studies. The studies were comprehensively investigated, well characterised, and generally of good quality, with pivotal studies conducted in accordance with GLP and the relevant CVMP guideline on the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/1999). The majority of studies used laboratory Beagles, but assessments were also made in mixed breed animals. The age of study animals ranged from

8 weeks to 7 years. Pharmacokinetic assessments have been made in the fed and fasted states. Repeat-dose pharmacokinetics following 10 consecutive monthly administrations were also determined. Studies were most often conducted at the recommended minimum target dose of 2 mg/kg bw, but the pharmacokinetics of sarolaner up to 20 mg/kg bw have also been investigated.

Bioavailability was high at more than 85%. Plasma protein binding was determined in vitro and calculated at ≥99.9%. A distribution study determined that ^{14}C-Sarolaner-related residues were widely distributed to the tissues. Sarolaner has low clearance (0.12 ml/min/kg bw) and a moderate volume of distribution (2.81 l/kg). The half-life was comparable for the intravenous and oral routes at 12 and 11 days, respectively.

The depletion from tissues was consistent with the plasma half-life. The primary route of elimination is biliary excretion of the parent molecule, with minor contributions from metabolic clearance.

Plasma exposure was dose proportional in dogs when given a single dose from the intended recommended therapeutic dose (RTD) of 2–4 to 20 mg/kg bw. There is potential for some accumulation upon repeat dosing. Based on the pharmacokinetic analyses conducted in the context of the pivotal target animal safety study, the applicant concludes that the maximum observed plasma concentration (C_{max})reaches a plateau following approximately 3–5 doses, and exposure, as determined by $AUC_{0-\tau}$, reaches a plateau following 6–7 doses for $AUC_{0-\tau}$.

The effect of feeding on bioavailability was determined using parallel design studies. The extent of absorption, as characterized by $AUC_{0\text{-}3\ days}$, was comparable for the fed and fasted animals, hence it is concluded that prandial state does not affect the extent of absorption. C_{max} is higher, and t_{max} earlier in the fasted state; however, the shift in C_{max} and t_{max} dependent on the prandial state is not considered of clinical relevance (on this point, it is noted that the laboratory dose confirmation studies were conducted in fed dogs, and the GLP Margin of Safety study was conducted in fasted dogs). It is accepted that pharmacokinetic data support the dosing of sarolaner with or without food.

In general, PK differences for males versus females were not significant, and PK parameters for Beagles and mixed breeds are comparable, i.e. C_{max} of 1050 and 985 ng/ml, t_{max} 5.6 and 8.3 hours, and $AUC_{0\text{-}35d}$ of 333 and 387 µg.hr/ml, respectively. PK parameters C_{max} and $AUC_{0\text{-}28\ days}$ are lower for Beagle puppies at 8 weeks of age (C_{max} 457 ng/ml, $AUC_{0\text{-}28\ days}$ 134 µg.hr/ml) compared with adult (6–14 months) Beagles (C_{max} 937 ng/ml, $AUC_{0\text{-}28\ days}$ 265 µg.hr/ml). In considering efficacy over the entire dosing interval, $t_{1/2}$ and the plasma concentration at the end of the dosing interval ($C_{28\ days}$) are most important. Though mean $t_{1/2}$ and $C_{28\ days}$ values are lower for puppies than for adults, it is noted that the low end of the ranges for $t_{1/2}$ and $C_{28\ days}$ values are comparable for 8-week-old puppies and adults. On this basis, it is accepted that the differences in systemic exposure should not negatively impact on efficacy.

The product is highly bound to plasma proteins and might compete with other highly bound substances. A warning to this effect is included in section 4.8 of the SPC.

Dose determination / justification

A total of three exploratory dose determination studies were conducted in ticks and fleas to identify the least susceptible parasite (for study design, see below under “dose confirmation”). The susceptibility of parasites tested could be divided into three clusters: “highly susceptible” to 20–30 ng/ml (*I. ricinus, C. felis* and *R. sanguineus*), “medium susceptible” to approximately 50 ng/ml (*D. variabilis*), and “less susceptible” to 70–80 ng/ml (*A. maculatum* and *D. reticulatus*).

Further studies showed that for the least sensitive tick species, *D. reticulatus* and *A. maculatum*, the EC_{90} (i.e. concentration required to achieve 90% of the maximum effect) was 63 ng/ml (95% CI: 42, 84) and

80 ng/ml (95% CI: 57, 103), respectively. A population pharmacokinetic model was used to simulate plasma concentrations at a single dose at 1, 1.5 and 2 mg sarolaner/kg. A dose of 2 mg/kg bw was chosen as the minimal effective sarolaner dose, as only this dose predicted a concentration above the threshold of 80 ng/ml in 95% of dogs for a month.

The pivotal dose determination study using *A. maculatum* investigated doses of 1, 2 or 4 mg sarolaner/kg bw. A dose of 2 mg/kg was required to achieve the required 90% efficacy threshold for up to 28 days post-treatment.

When selecting the dose, the applicant also took into account the speed of kill. Based on the data presented, a dose of 2 mg/kg was required to achieve rapid kill in *I. ricinus* (within 12 hours) and to maintain this for a period of one month.

Specific dose finding studies in regard to mites were not conducted; however, dose confirmation studies confirmed efficacy against the scabies mite. This approach was considered acceptable.

The CVMP considered that the recommended minimum treatment dose of 2 mg sarolaner/kg bw was satisfactorily justified to achieve the intended immediate kill for ticks, fleas and mites and to maintain this effect for one month.

Target animal tolerance

The target animal safety for sarolaner has been investigated in several studies including the pivotal target animal safety study; as well as an exploratory tolerance study in puppies, an exploratory margin of safety study in dogs (non-GLP), and a pilot escalating dose tolerance study in adult dogs. In addition, a study was conducted to evaluate safety of sarolaner when administered to avermectin-sensitive Collie dogs.

The pivotal target animal safety study was conducted in accordance with GLP and VICH GL43. The study used the final formulation and evaluated tolerance in 8-week-old puppies. Based on the results of this study, sarolaner chewable tablets, when administered at 4, 12 or 20 mg/kg bw (1X, 3X, and 5X the maximum recommended therapeutic dose, RTD) once monthly over a 9-month period (10 consecutive doses) to 8 week old Beagle puppies, was generally well tolerated; however, neurological effects were noted at doses of 12 mg/kg (3X RTD; tremors, ataxia) and 20 mg/kg (5X RTD; convulsions, tremors and ataxia). Signs appeared to occur primarily in the first 24 hours after dosing and resolved without treatment. Early during the research phase, results from a safety study also indicated that a high oral dose (62.5 mg/kg bw) caused effects in dogs on the nervous system (convulsions), and also, in another non-GLP pharmacokinetic study a single dog (out of six) exhibited neurological signs after the third dose of 12 mg sarolaner/kg bw. Analysis of the samples collected for pharmacokinetic assessment showed unexpectedly high plasma concentrations for this specific dog.

Nervous system signs appear in a proportion of dogs at 3X the maximum RTD (12 mg/kg) and generally manifest as tremors. At 5X (20 mg/kg), the signs may be more severe (including convulsions) and tend to occur within the same dog at the beginning of the treatment and then do not recur later. No adverse neurological symptoms have been seen in dogs administered sarolaner at the recommended treatment dose of 2–4 mg/kg bw.

Increased plasma exposures frequently accompany neurological signs; however high plasma concentrations are not necessarily predictive of neurological signs. It would appear that certain dogs are more sensitive than others.

Regarding the mechanism for the reported neurological events, it is considered that these events are directly related to the pharmacology of the isoxazoline class of compounds.

A review of all relevant safety data from field and laboratory studies, concluded that while neurological events attributable to treatment were observed on occasion in overdosed dogs, such signs (attributable to treatment) were not observed at the recommended dose of 2–4 mg/kg. Having considered the individual animal data provided from the large number of animals investigated, the CVMP accepted that neurological events recorded in animals treated at the recommended dose (2–4 mg/kg) are unlikely to be treatment-related. However, the risks related to overdose in the target animal are included in section 4.10 of the SPC.

Apart from the neurological effects the target animal safety studies did not result in other toxicological findings of concern. In the various confirmatory and field efficacy studies conducted, sarolaner was generally well tolerated.

In addition, a study was conducted to evaluate the safety of sarolaner when administered to avermectin-sensitive Collie dogs (MDR1 -/-). No treatment-related effects were observed in Collie dogs treated with up to 3X RTD when observed over a 2 day period.

Based on all the data provided, the CVMP concluded that sarolaner at the recommended dose is well-tolerated. Risks related to overdose in the target animal are included in section 4.10 (overdose) of the SPC.

Clinical Studies

Laboratory studies (Dose confirmation)

The applicant provided a large number of laboratory dose confirmation studies, with at least 2 studies per parasite for most parasite species, which were conducted in the EU, US and/or other regions. The confirmatory efficacy studies are grouped by parasite and claim type into four groups: flea efficacy, tick efficacy, disease transmission prevention, and mite efficacy. With the exception of the exploratory dose determination studies, all studies were conducted according to the standards of VICH GCP.

In most clinical studies Simparica chewable tablets or a comparable prototype were used. All studies were conducted using the same basic design as detailed in the CVMP guideline on testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMA/CVMP/EWP/005/2000-Rev.2).

Group allocation was by ranking the dogs by descending parasite infestation rates and random allocation to the study groups, including at least 8 dogs (adults, usually Beagle dogs or purpose-bred cross-breeds) in each treatment group. Dogs received either a single oral dose of 2 mg sarolaner/kg bw, or a negative control (placebo), expect for one study against *Demodex canis*, which used a positive control group (fixed combination containing imidacloprid and moxidectin) for welfare reasons.

Fleas:

Flea infestations (*C. felis, C. canis)* were conducted 24 hours before treatment administration, and weekly after treatment administration (up to eight weeks, depending on the study), by placing approximately 100 adult unfed fleas directly on each dog. Dogs were kept still for several minutes to allow fleas to disperse and settle. Typically, flea comb counts that covered the entire body surface of the animals were conducted approximately 24 hours after treatment administration (on Day 0) and 24 hours after each subsequent weekly infestation. Each animal was combed for at least 10 minutes and all fleas recovered during the combing were removed from the animals. The flea isolates originated from the field and were multiplied in vivo (i.e. on host animals) in the laboratory.

The studies confirmed that sarolaner, administered at a dose of 2 mg/kg bw in a series of laboratory dose confirmation studies, demonstrated efficacy in the treatment of flea infestation by exceeding the required threshold of 95% at all time points up to and including 35 days (5 weeks).

In addition to the standard dose confirmation laboratory studies, two studies were conducted to characterize the *speed of kill* (immediate insecticidal efficacy) of sarolaner against *C. felis* following the initial treatment and each weekly re-infestation for 5 weeks. In these studies, fleas were counted at time points between 1 and 12 hours following treatment on Day 0, and after subsequent weekly flea infestations. In both speed of kill studies, more than 95% of the fleas were killed within 8 hours on the day of treatment, and this effect (>95% kill within 8 hours) was maintained until Day 21. While the efficacy threshold of 95% kill within 8 hours was not achieved at Day 28 in one of the two studies presented, the reported efficacy of 93.9% at this day was very close to the required threshold. Taking all data together, the CVMP therefore agreed that an onset of efficacy of "within 8 hours" for fleas (*C. felis*) could be accepted.

An additional study investigating the efficacy of repeated monthly oral administrations of a minimum dose of 2 mg sarolaner/kg bw to Beagle dogs (6–8 months) demonstrated efficacy in the treatment of pre-existing *environmental flea infestations* under simulated home environmental conditions.

The CVMP also noted that sarolaner killed adult fleas before they had an opportunity to lay eggs, thus *reducing the risk of environment contamination* with fleas in areas to which the dog has access.

Ticks:

A number of laboratory dose confirmation studies in ticks were submitted, including *Dermacentor reticulatus, D. variabilis, Rhipicephalus sanguineus, Ixodes ricinus, I. scapularis, I. hexagonus, I. holocyclus, Amblyomma americanum,* and *A. maculatum.* Tick infestations were conducted 48 hours before treatment started and continued weekly by placing approximately 50 viable, adult unfed ticks of the respective species directly on each dog. All tick isolates originated from the field and were multiplied in vivo (i.e. on host animals) in the laboratory. The ticks were applied to the dorsal area of the dog. Dogs were sedated for the tick infestations to allow ticks to disperse and attach. Up to 48 hours following treatment administration (on Day 0) or infestations, tick counts were conducted that covered the entire body surface of the animals. Each animal was searched for at least 10 minutes and all ticks recovered were removed from the animals.

The assessment of efficacy was based on the percent reduction in the arithmetic mean (live parasite counts relative to control) using the recommended Abbott's formula. However, for ticks, the approach for efficacy assessment used by the applicant differs from that detailed in the current CVMP guideline (EMEA/CVMP/EWP/005/2000-Rev.2) and simplifies the categorization of ticks into alive and dead (i.e. does not take into account attachment or engorgement status), with assessment of acaricidal activity based on a comparison of the number of live ticks in untreated control animals compared to those on treated dogs at the same time point. The CVMP accepted this approach already in the context of the assessment of other recent applications for orally administered systemically active acaricides, and implemented this approach also in the recently revised (Rev.3, not yet finalised) revision of the CVMP guideline (EMEA/CVMP/EWP/005/2000). However, the SPC (section 4.2) and package leaflet (section 4) therefore clearly states that the use of the product is for treatment only (not preventive use), and that parasites must attach to the host and commence feeding in order to be exposed to the active substance. Given that parasites need to start feeding on the host to become exposed to the active substance, a statement is also included (sections 4.4 and 12 of the SPC and package leaflet respectively) that the risk of the transmission of parasite-borne diseases cannot be excluded.

The comprehensive package of confirmatory laboratory studies showed an immediate (on Day 2) acaricidal efficacy of sarolaner against all tick species of at least 99.5% and a residual efficacy of at least 94.5% for 35 days after treatment. Based on the data presented, the CVMP concluded that the studies were adequate to support the efficacy of sarolaner against the following tick species: *Amblyomma americanum, A. maculatum, Dermacentor reticulatus, D. variabilis, Ixodes ricinus, I. hexagonus, I. scapularis* and *Rhipicephalus sanguineus*. For *I. holocyclus*, dose confirmation studies were not adequate to support efficacy.

In addition to the standard dose confirmation laboratory studies, a pivotal study was conducted to characterize the *speed of kill* of sarolaner against *I. ricinus* following the initial treatment and each weekly re-infestation for 5 weeks. Three additional speed of kill studies against *I. scapularis* and/or *A. maculatum* were submitted. In these studies, ticks were counted at time points between 4 and 48 hours following treatment on Day 0, and after subsequent weekly tick infestations. In the pivotal speed of kill study, sarolaner started killing ticks as early as 8 hours following treatment administration; an adequate level of efficacy above the required 90% was only achieved by 12 hours after infestation. It is noted that the speed of kill study investigated efficacy in only one tick species, *I. ricinus*, which is classified as highly susceptible to sarolaner. It is reasonable to assume that speed of kill will vary for tick species depending on their susceptibility to sarolaner. However, the text on speed of kill proposed for inclusion in the SPC can be accepted in that it refers to *I. ricinus* specifically (that is, it is not generalized to all tick species). It is accepted that ticks are killed within 12 hours of attachment, but that ticks on the animal prior to treatment may not be killed until 24 hours after treatment, which is reflected in the wording of section 5.1 of the SPC: "For ticks (*I. ricinus*), the onset of efficacy is within 12 hours of attachment during the 28 day period after product administration. Ticks on the animal prior to administration are killed within 24 hours."

Reduction of transmission of tick-borne diseases:

In support of the proposed indication for the treatment indirectly to reduce the risk of transmission of tick-borne diseases (canine babesiosis, borreliosis and anaplasmosis) from infected ticks for 4 weeks, the applicant presented 2 GCP-compliant controlled studies conducted in dogs to evaluate the efficacy of sarolaner to prevent the transmission of tick borne disease pathogens *Babesia canis*, *Borrelia burgdorferi* and *Anaplasma phagocytophilum*.

A third GCP-compliant controlled study was conducted in dogs to evaluate the efficacy of sarolaner to prevent the transmission of tick-borne disease pathogen *Ehrlichia canis* which is, however, not in the scope of this application.

Efficacy was assessed at the end of the one month treatment period by infesting dogs with infected ticks at 21 and 28 days after treatment with sarolaner. Polymerase chain reaction (PCR) analysis of ticks that were used for infestation confirmed that a high percentage of ticks carried the investigated pathogens (25% of the ticks were infected with *B. canis*, 57% were positive for *B. burgdorferi*, 6.7% were positive for *A. phagocytophilum* and 24% of the ticks were infected with *E. canis*). At various time points up to between 6 and 8 weeks (depending on the study) following tick infestation, appropriate samples were collected for PCR analysis and for detection of antibodies to the infective agent under test. In addition, each test animal was examined for clinical signs of disease.

Under the conditions of studies conducted, a single treatment with 2 mg/kg sarolaner administered orally 21 or 28 days prior to infestation with disease-infected ticks prevented infection with *B. canis* and transmission of *B. burgdorferi* and *A. phagocytophilum.* However, while treated dogs did not develop clinical signs of infection associated with *B. canis*, transmission of the infective agent was not prevented.

In addition, treatment did not protect animals from/prevent *E. canis* infection, however this is not relevant for this application.

Also, while CVMP accepted that there is generally a brief delay in transmission of infectious organisms after tick attachment, the process of transmission of infectious agents is open to numerous variables that can impact on transmission times, and transmission of infective agents may occur within 12–24 hours after attachment (the time required to achieve ≥90% kill). In addition, there is evidence that partially fed infected (during larval feeding) ticks could reattach to a new host and rapidly transmit infectious agent during a second feeding period, and ticks might readily migrate between dogs.

Taking all of the above into account, an indication for a reduction in the risk of transmission of tick-borne diseases could not be accepted for this product based on the available data.

Mites:

Efficacy of sarolaner against the most common mites infesting dogs, *Sarcoptes scabiei, Demodex canis* and *Otodectes cynotis* was evaluated in three separate laboratory dose confirmation studies from South Africa.

For the *Sarcoptes scabiei* and *Demodex canis* dose confirmation studies, dogs with natural infestations were used. Mixed breed dogs from a wide range of age and bodyweights were administered the test product on either 2 (*S. scabiei*) or 3 occasions (*D. canis*) at monthly intervals. For *Otodectes cynotis*, infections were induced (approximately 100 mites were transferred into each of the ears of recipient dogs before study start) and the test product was administered to different groups of dogs on a single occasion or twice at an interval of one month. For all three studies, efficacy was evaluated at various time points up to 30 days after the last treatment. The primary efficacy endpoint was the percent reductions in live mite counts relative to the placebo control group. The clinical response to treatment was also evaluated.

Monthly treatment with sarolaner (2 mg/kg bw) resulted in a marked reduction in *Sarcoptes scabiei* mites (≥99.9% with 2 monthly treatments). In addition, efficacy was evaluated in a multi-centre clinical field study against *Sarcoptes scabiei* in the EU (see below). The results of the EU field study, supported by the results of the laboratory dose confirmation study, indicate that two treatments with sarolaner (2–4 mg/kg in a chewable tablet) administered one month apart were safe and effective in the treatment of sarcoptic mange, with elimination of live mite infestation and reduction in clinical signs after the second treatment. The proposed indication was therefore accepted.

Results showed that three treatments at monthly intervals with sarolaner (2 mg/kg bw orally) was effective at eliminating *Demodex canis* infestation in the study population tested. A single-dose of sarolaner (2 mg/kg bw) resulted in a 98.7% reduction in ear mites (*Otodectes cynotis* infestations), and two doses administered at an interval of one month resulting in a 99.9% reduction in ear mites. However, the data provided for these two mites were very limited (a single study in a laboratory setting using a relatively low number of test animals). Given that *Demodex canis* and *Otodectes cynotis* represent major indications, it is considered that the available dataset is inadequate to support the inclusion of an indication in section 4.2 of the SPC for this new active substance. However, the CVMP accepted that reference to activity against *Demodex canis* and *Otodectes cynotis* could be included in section 5.1 of the SPC.

Field studies

The applicant conducted three field studies in Europe to evaluate the efficacy and safety of Simparica chewable tablets at the recommended dosage of 2 to 4 mg/kg, administered orally to dogs at monthly intervals for three months, in the treatment and control of natural infestations of fleas, ticks or sarcoptic

mange (a separate study for each category of parasite). All three studies were conducted in accordance with the VICH GL7 (GCP) and were designed as randomised, single blinded, multi-centre studies where efficacy was evaluated against an appropriate positive control. Each study was conducted using multiple sites in up to 6 Member States. For all studies, the test population is considered representative of the target population.

In addition, a field study conducted in the USA evaluating efficacy against fleas is submitted as supportive data. This study used a similar study design as the EU flea study.

Fleas:

The findings of the dose confirmation studies were confirmed by a European multicentre field study conducted in the United Kingdom, France, Hungary, Belgium and Italy in 2013. The primary objective was to demonstrate the efficacy and safety of Simparica chewable tablets in the treatment and control of natural infestations of fleas (*C. felis* and *C. canis*) on dogs presented as veterinary patients in Europe. The primary efficacy end point was the percentage reduction in live flea counts from baseline at the post-treatment time points. Secondary objectives were to evaluate the efficacy of sarolaner in the reduction of clinical signs associated with flea allergy dermatitis (FAD), and the palatability of Simparica chewable tablets.

Simparica chewable tablets were administered by the animal owner with or without food, and the voluntary consumption of the tablets was assessed by the owner. Dogs (purebred and crossbreeds) of at least 14 weeks of age (up to approx. 15 years) and weighing at least 3.9 kg (up to approx. 65 kg) that were infested with at least 5 live fleas were enrolled, and treated either with the recommended dose of 2 to 4 mg/kg bw sarolaner (n=189) administered orally at monthly intervals for three months, or an authorised positive control containing spinosad (n=96). Flea counts and clinical signs were monitored at Day 0, 14, 30, 60 and 90.

Efficacy results showed that sarolaner was demonstrated to be non-inferior to a positive control product, and effective against the claimed flea species (*C. felis* and *C. canis*). Over the course of the study, there was a reduction in the numbers of animals with clinical signs of FAD in both study groups. Regarding safety, sarolaner was well tolerated: no adverse events attributable to treatment were recorded.

Based on the results of this study, the CVMP accepts that under natural conditions a single oral dose of sarolaner (2–4 mg/kg bw) administered on a monthly basis, is efficacious for the treatment of flea infestation (e.g. *Ctenocephalides canis*, *C. felis*) and no safety concerns were identified.

These results were further supported by the results of a supplementary US field study.

Ticks:

Regarding those tick species for which satisfactory laboratory dose confirmation data have been provided, EU field data are only available for *Dermacentor reticulatus, Ixodes hexagonus, Ixodes ricinus* and *Rhipicephalus sanguineus*. A European field study was provided investigating the efficacy and safety of Simparica chewable tablets in the treatment and control of natural infestations of ticks on dogs presented as veterinary patients in Europe. The study was conducted in 2014 in the United Kingdom, France, Hungary, Belgium and Italy. Dogs of various breeds ranging in age (0.2 to 17 years) and weight (2.9 to 66.5 kg bw) and infested with at least 3 live attached ticks (*Rhipicephalus sanguineus*, *Dermacentor reticulatus, Ixodes ricinus* or *I. hexagonus*) received either sarolaner at the recommended dose of 2 to 4 mg/kg, orally at monthly intervals for 3 months (n=122), or an authorised positive control containing fipronil (n=59). Dogs were checked for ticks at day 0, 14, 30, 60, and 90.
The primary efficacy end point was the percentage reduction in live tick counts from baseline at the

post-treatment time points over all tick species combined. A secondary objective was to evaluate the palatability of the Simparica chewable tablets.

The study showed that Simparica when administered at the recommended dose to dogs under field conditions was effective against ticks (*Ixodes ricinus*, *Rhipicephalus sanguineus*, *Dermacentor reticulatus* and *Ixodes hexagonus*). Based on the primary efficacy parameter sarolaner was confirmed to be non-inferior to the control product. Regarding safety, the chewable tablets were well tolerated.

Based on the results of this study, the CVMP considered that under natural conditions a single oral dose of sarolaner, administered on a monthly basis, is efficacious for the treatment of tick infestation (*Ixodes ricinus*, *Rhipicephalus sanguineus*, *Dermacentor reticulatus* and *Ixodes hexagonus*) under natural conditions, and no safety concerns were identified.

Mites:

The efficacy of sarolaner at the recommended dosage of 2 to 4 mg/kg, administered orally at monthly intervals for two months in the treatment of dogs (n=53) with natural infestations of *Sarcoptes scabiei*, was evaluated in a multi-centre European (United Kingdom, France, Hungary, Belgium, Spain and Italy) clinical field study in 2013-2014, and compared to a positive control (n=26, moxidectin and imidacloprid). The mean age of the dogs (mixed breeds and purebreds) at enrolment was approximately 4 years, and the mean body weight was approximately 18–22 kg.

The primary objective was the parasitological cure rate, which was defined as the percent of dogs free of live mites in the skin scrapings, calculated at each post-treatment time point. The secondary efficacy endpoint was the frequency distribution of the skin lesion severity grades at each post-treatment time point. In addition, palatability of the sarolaner chewable tablets was assessed.

The results indicate that two treatments with sarolaner (2–4 mg/kg in a chewable tablet) administered one month apart was effective in the treatment of sarcoptic mange, with elimination of live mite infestation and reduction in clinical signs after the second treatment, and no safety concerns were identified. The proposed indication was therefore accepted by the CVMP.

However, no field data were presented for other mite species. Given that *Demodex canis* and *Otodectes cynotis* represent major indications, it is considered that the available data (laboratory studies, see above) are inadequate to support the inclusion of an indication in section 4.2 of the SPC for this new active substance. Current CVMP guidelines for both anthelmintics and ectoparasites recommend that for new substances all indications should be supported by clinical field data. However, the CVMP accepted that reference to activity against *Demodex canis* and *Otodectes cynotis* could be included in section 5.1 of the SPC.

Target animal safety in field studies:

In the various confirmatory and field efficacy studies conducted, sarolaner was generally well tolerated. In placebo controlled studies, the overall incidence of adverse effects is similar between animals administered sarolaner and those administered placebo.

Other studies

Palatability was investigated in three EU field studies. The test item was administered on 835 occasions in the flea field study, on 445 occasions in the tick field study and on 158 occasions in the *Sarcoptes* field study. All treatment administrations took place in the home environment and the tablets were offered to all dogs without any food/treats. Voluntary consumption (full consumption within one minute) exceeded 90%; therefore, it is accepted that the test item is palatable. The assessment of palatability was in line

with the CVMP guideline on the demonstration of palatability of veterinary medicinal products (EMA/CVMP/EWP/206024/2011).

Overall conclusion on efficacy

A comprehensive efficacy dataset has been provided.

Pharmacodynamics: sarolaner is a potent inhibitor of the GABA receptor function with a high binding to arthropod receptors, blocking pre- and post-synaptic transfer of chloride ions across cell membranes. This results in uncontrolled activity of the central nervous system of fleas, ticks and mites and their death. Binding of sarolaner to mammalian GABA receptors is expected to be low.

Pharmacokinetics: following oral administration, sarolaner is rapidly absorbed. It has low plasma clearance and a moderate volume of distribution, with a plasma half-life of 12 days. The main route of elimination is via faeces. Sarolaner is highly bound to plasma proteins and might compete with other highly bound substances.

Dose finding: based on a range of dose finding studies in fleas and ticks, a single oral dose of 2 mg/kg of sarolaner was chosen as the minimal efficacious dose over a period of 28 days.

Tolerance: in general, Simparica chewable tablets were well tolerated when administered at the recommended treatment dose of 2–4 mg/kg. However, neurological signs were seen in dogs treated at 3X the maximum RTD (12 mg/kg), generally manifest as tremors.

Palatability: palatability of the product was investigated and confirmed as part of the EU field trials.

Efficacy: a single dose of sarolaner (2–4 mg/kg bw) showed efficacy up to 5 weeks after treatment for fleas (*C. felis*, *C. canis*) and some of the claimed tick species (*Ixodes ricinus, Ixodes hexagonus, Dermacentor reticulatus* and *Rhipicephalus sanguineus)*. Two treatments with sarolaner (2–4 mg/kg bw) at monthly intervals were effective in the treatment of sarcoptic mange.

However, there are insufficient efficacy data to support certain proposed indications (*D. canis* infestation, *O. cynotis* infestations, reduction in the risk of transmission of tick-borne diseases) which, therefore, cannot be accepted.

Part 5 – Benefit-risk assessment

Introduction

Simparica chewable tablets contain as the active substance sarolaner, a new active substance which is not yet authorised as a veterinary medicinal product in the Community. The tablets are presented in strengths of 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 120 mg, packaged in aluminium blister packs. The secondary packaging is a cardboard carton containing 1, 3 or 6 tablets. The route of administration is oral use.

The product is intended for the treatment of tick, flea and mite infestations in dogs and can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis.

This is a full application submitted in accordance with Article 12(3) of Directive 2001/82/EC.

Benefit assessment

Direct therapeutic benefit

Sarolaner is a potent insecticide and acaracide.

When administered orally to dogs at the recommended dose (2–4 mg/kg bw), there is immediate efficacy against fleas (*Ctenocephalides felis*) within 8 hours after treatment. Efficacy persists for at least 5 weeks.

For ticks (*Ixodes ricinus*), the onset of effect is within 12 hours of attachment. (Ticks on the animal prior to administration of the product are killed within 24 hours.) Efficacy persists for at least 5 weeks.

For sarcoptic mange mites (*Sarcoptes scabiei*), two treatments with the product, administered one month apart, is effective in the treatment of sarcoptic mange, with elimination of live mite infestation and reduction in clinical signs after the second treatment.

In conclusion, well conducted studies support the benefits of Simparica which are its efficacy in the treatment of tick infestations (*Dermacentor reticulatus, Ixodes hexagonus, Ixodes ricinus* and *Rhipicephalus sanguineus*), the treatment of flea infestations (*Ctenocephalides felis* and *Ctenocephalides canis*), the treatment of sarcoptic mange (*Sarcoptes scabiei*), and as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD).

Additional benefits

The effective control of fleas on treated dogs will reduce the risk of infestation of other animals in contact with infested dogs.

Simparica chewable tablets may be administered by the animal owner at home. The presentation is a chewable tablet formulation which has been designed to be palatable for most dogs. The method and route of administration of the product may be considered an additional benefit in that there is limited potential for the user to be exposed to the active substance.

Risk assessment

Main potential risks have been identified as follows:

Quality:

The formulation, manufacture, control and stability of the finished product is well described and specifications set will ensure that product of consistent quality will be produced. There are a number of recommendations relating to the quality of the product but these do not preclude the conclusion that the quality of the product is acceptable.

For the target animal:

The safety of Simparica has been investigated in healthy dogs when used according to the proposed dosing recommendations. The product was found to be well tolerated by animals treated with the recommended treatment dose of 2–4 mg sarolaner/kg bw. However, at overdoses (3X RTD or more) neurological effects (tremor, ataxia, convulsions) were observed.

No data were submitted on reproductive toxicity in the target species and this is addressed in the product information.

For the user:

The risk to the user is considered acceptable noting in particular that the pharmaceutical form (chewable tablet) limits the potential for the user to be exposed to the active substance when removing the product from the packaging and administering the tablet to the animal; the tablet is presented in child-resistant packaging; and the product information includes a warning advising of the potential for adverse effects in case of accidental ingestion and specific instructions to remove tablets from the packaging only when required, and to store the product out of the sight and reach of children.

The CVMP concluded that user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

For the environment:

Simparica is for the individual treatment of companion animals. The product is not expected to pose a risk for the environment when used in accordance with the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user and environment and to provide advice on how to prevent or reduce these risks.

User safety risks have been identified, mainly concerning the risks associated with exposure in children. This risk is managed by the presentation of the product in primary packaging which has been demonstrated to be child-resistant and by the inclusion of appropriate advice in the SPC.

Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall.

The benefit of Simparica is its efficacy in the treatment of flea, tick and mite infestations in dogs for up to 5 weeks.

The formulation and manufacture of the product is well described and the proposed specifications would ensure that product of consistent quality will be produced.

At the recommended dose, it is well tolerated by the target animals.

The product represents an acceptable risk for the user, the target animal and the environment when used as recommended; and appropriate warnings have been included in the SPC.

Conclusion on the benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and product literature.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Simparica is approvable since these data satisfy the requirements for an authorisation set out in the legislation

(Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.