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SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

Final CVMP assessment report for LONGRANGE (EMEA/V/C/004291/0000)

International non-proprietary name: eprinomectin

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

The applicant MERIAL submitted on 13 December 2016 an application for a marketing authorisation to the European Medicines Agency (The Agency) for LONGRANGE, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 8 October 2015 as the applicant showed that the product would provide a significant technical innovation.

LONGRANGE is a prolonged-release solution for injection containing eprinomectin, an avermectin, which binds selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve or muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of endo- and ectoparasites.

Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA). The target species is cattle and the route of administration is subcutaneous use.

The applicant applied for the following indication(s):

Treatment of the following parasites:

- Gastrointestinal roundworms (Adult and L4): *Ostertagia ostertagi/lyrata, Cooperia oncophora/surnabada, C. punctata, Haemonchus contortus, Trichostrongylus axei, T. colubriformis, Bunostomum phlebotomum, Nematodirus helvetianus, Oesophagostomum radiatum.*
- Lungworm (Adults and L4): *Dictyocaulus viviparus;*
- *Ectoparasites:* Warbles (parasitic stages: *Hypoderma bovis, H. lineatum), m*ange mites (*Sarcoptes scabiei* var. *bovis*); lice (*Linognathus vituli, Haematopinus eurysternus, Solenoptes capillatus)* and horn flies (*Haematobia irritans).*

Prevention of reinfections with the following parasites:

- Gastrointestinal roundworms: *Ostertagia ostertagi/lyrata, Trichostrongylus colubriformis, Haemonchus contortus*, *Bunostomum phlebotomum, Oesophagostomum radiatum, Cooperia oncophora/surnabada, C. punctata, Trichostrongylus axei.*
- Lungworms: *Dictyocaulus viviparus*

LONGRANGE prolonged-release solution for injection for cattle contains 50 mg/ml eprinomectin. The product is available in multi-dose amber glass vials and in three different pack sizes, containing 50 ml, 250 ml or 500 ml.

The rapporteur appointed is Wilhelm Schlumbohm and the co-rapporteur is Bruno Urbain.

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

In the light of the overall data submitted and the scientific discussion within the CVMP, a negative opinion for LONGRANGE was adopted by the CVMP during their meeting in June 2018.

Scientific advice

The applicant received scientific advice from the CVMP on 11 December 2014 and 4 June 2015. The first scientific advice pertained to safety (ecotoxicity and residues) and the clinical development of the dossier (dose confirmation, target animal safety), and the second to safety (residues). The CVMP's scientific advices were largely followed by the applicant.

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 (Version 2.0, dated 19 Aug 2015) which fulfils the requirements of Directive 2001/82/EC, as amended. 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

Manufacture of the dosage form takes place outside of the EEA. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture and batch release of such veterinary dosage forms, has been provided. Batch release takes place within the EU. A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site.

Overall conclusions on administrative particulars

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

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The finished product is a clear to amber, non-aqueous solution for injection containing 50 mg eprinomectin per ml as the active substance.

Other ingredients are butylhydroxytoluene (BHT) as an antioxidant, poly (lactic-*co*-glycolic) acid (PLGA), N-methylpyrrolidone (NMP) and triacetin. All-*rac*-alpha-tocopherol (vitamin E) is present in small quantities since it is added to eprinomectin as antioxidant. Nitrogen is used as a head space blanket during manufacture.

The product is presented in 50 ml, 250 ml and 500 ml type I amber glass bottles with chlorobutyl rubber stoppers and aluminium caps.

Containers

The primary packaging for all vial sizes is a Ph. Eur. type I amber glass vial closed with a Ph. Eur. type stopper and an aluminium cap. All test parameters comply with the relevant Ph. Eur. methods with reference to the USP for some methods.

The choice of the container-closure system has been validated by stability data and is adequate for the intended use of the product.

The product is marketed in an outer cardboard carton containing one vial of 50 ml, 250 ml or 500 ml solution for injection. The pack sizes are consistent with the dosage regimen and duration of use.

Development pharmaceutics

The aim was to develop a prolonged-release solution for injection for cattle, containing eprinomectin as the active substance. Except for the poly (lactic-*co*-glycolic) acid, all excipients are well known pharmaceutical ingredients and their quality is compliant with the respective Ph. Eur. USP standards. The list of excipients is included in section 6.1 of the SPC.

The formulation used during clinical studies was identical to the proposed formulation. The corresponding certificates of analysis show compliance with the proposed finished product specifications.

Extensive development work has been performed with regard to the novel excipient poly (lactic-*co*-glycolic) acid. The choice of the manufacturing process has been justified taking into account the Annex to the CVMP note for guidance on development pharmaceutics: decision trees for the selection of sterilisation methods (EMEA/CVMP/065/99).

The compatibility of the packaging material with the proposed formulation has been confirmed.

Incompatibility of the formulation with polycarbonate-containing (dosing) devices has been noticed and hence polycarbonate containing materials should be avoided during the manufacture, testing and end-use of the product.

Method of manufacture

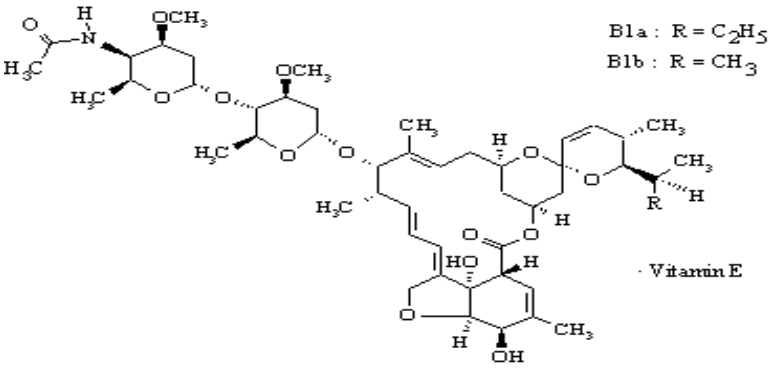
The manufacturing process consists of three main steps: compounding, pre-filtration and sterilising filtration, aseptic filling into the glass vials and packaging. The process is considered to be a non-standard manufacturing process. Critical steps have been identified and adequate in-process controls for this solution for injection are performed. The proposed limit for bioburden prior to sterile filtration is in line with the requirement of not more than 10 cfu/100 ml.

Major steps of the manufacturing process have been validated using three commercial scale batches with regard to mixing times, filter integrity, bioburden, bulk holding times and fill volume. It has been demonstrated that the manufacturing process is capable of producing the finished product at the intended quality in a reproducible manner. Additional information on the validation of the sterilising filtration and on the aseptic processing, and analytical data to justify the bulk holding times have been provided.

Control of starting materials

Active substance

The active substance eprinomectin is a mixture of the two components B1a and B1b. The chemical name of component B1a is (4''R)-4"-(acetylamino)-5-O-demethyl-4''-deoxyavermectin A1a, and of component B1b is (4''R)-4"-(acetylamino)-5-O-demethyl-25-de(1-methyl-propyl)-4''-deoxy-25-(1-methylethyl)averme ctin A1a. Due to its susceptibility to oxidative degradation, vitamin E is added to eprinomectin. The active substance has the following structure:



The active substance is a white to off-white crystalline hygroscopic powder with limited solubility in water. Eprinomectin exhibits stereoisomerism due to the presence of 20 (B1a) or 19 (B1b) chiral centres. The specific optical rotation of eprinomectin is routinely controlled. Polymorphism has not been observed for eprinomectin.

The information on the active substance is included in full detail within the dossier.

Eprinomectin is not subject of a monograph in either the European Pharmacopoeia (Ph. Eur.) or any other pharmacopoeia of the EU. The proposed specification is based on the USP monograph for eprinomectin.

The proposed specification is considered acceptable and the proposed limits are adequately justified. The analytical methods used have been sufficiently described and non-compendial methods appropriately validated in accordance with the VICH guidelines. These data are satisfactory and it can be concluded that the methods are suitable for the intended use. Satisfactory information regarding the reference standard used for assay has been presented.

Detailed information on the manufacture of the active substance has been provided.

Batch analysis data (n= 3 and industrial scale) of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

All tested parameters were within the specification.

The stability results indicate that the active substance is sufficiently stable. The stability results justify the proposed retest period.

Excipients

The excipients butylhydroxytoluene, N-methylpyrrolidone, triacetin and nitrogen are monographed in the Ph. Eur. and comply with their current monographs. Representative certificates of analysis are

enclosed for all excipients demonstrating compliance with the specifications. The information regarding the excipients described in a pharmacopoeia is generally acceptable.

Poly (lactic-*co*-glycolic) acid has not been previously included in any other veterinary medicinal products authorised in the EU. Therefore, this excipient is classified as a novel excipient.

Certificates of analysis from the excipient manufacturer and the manufacturer of the finished product have been provided. The in-house analytical methods used have been sufficiently described.

The results are in compliance with the proposed specification.

According to the CVMP guideline Excipients in the dossier for application for marketing authorisation for veterinary medicinal products (EMEA/CVMP/004/98) documentation of the chemistry is required for novel excipients. Information regarding the description of the process, the specifications of the starting materials, the impurity profile and the validation of analytical methods has been provided.

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

The product does not contain any materials derived from human or animal origin.

Control tests on the finished product

The product specification contains tests for appearance, clarity, colour, specific gravity, viscosity, identity and assay of eprinomectin, specified, unspecified and total related substances, drug release, butylhydroxytoluene content, sterility, bacterial endotoxins, water content, particulate matter, PLGA molecular weight and extractable volume. The specifications proposed for use at release are in general appropriate to control the quality of the finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with VICH guidelines. Satisfactory information regarding the reference standards used for assay of eprinomectin and BHT has been presented. For impurities testing, no reference standards are employed.

Batch analysis results are provided for three development batches and nine industrial scale batches confirming the consistency of the manufacturing process and its ability to manufacture Eprinomectin LAI to the intended product specification.

Stability

Stability data have been provided for three development batches three industrial scale batches and six industrial scale batches. These batches of finished product were stored under long term conditions for 24 months at 25 ºC/60% RH and for 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH guideline GL3. The batches of finished product are representative for those proposed for marketing and were packed in the primary packaging proposed for marketing.

The analytical procedures used are stability indicating. No significant changes have been observed and no differences between upright and inverted storage could be detected.

The three development batches were exposed to light as defined in the VICH guideline GL5 on photostability testing of new veterinary drug substances and medicinal products. After exposure to light the test product still met the specification however there was a notable increase in one impurity and a

decrease in antioxidant level. The product will be supplied in amber glass bottles (Type I). Temperature changes were not shown to be not detrimental for the quality of the finished product.

The in-use stability was examined in accordance with the CVMP Note for guidance: In-use stability testing of veterinary medicinal products (EMEA/CVMP/424/01) and the proposed in-use shelf life of 28 days with the storage conditions of 'Store below 30°C' is considered acceptable. Based on the available stability data, the proposed shelf-life of 24 months is acceptable. As stability tests of the commercial scale batches both under long term and under accelerated conditions did not show any significant changes, no temperature storage recommendation is required.

Overall conclusions on quality

In general, the dossier takes into account current rules and guidelines. The quality of this product is considered acceptable.

Part 3 – Safety

The application makes reference to the dossier and previous assessment of the CVMP in the context of the application for the establishment of maximum residues limits for eprinomectin in bovine species (see EPMAR - EMA/CVMP/779158/2015).

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Toxicological studies

The active substance eprinomectin was previously assessed by the CVMP in the context of the establishment of MRLs - see European Public MRL Assessment Report (EPMAR) (EMA/MRL/114/96-FINAL). The applicant submitted summaries of the MRL application, and the key findings of the toxicity studies evaluated are summarised below.

Single dose toxicity

Acute toxicity studies of eprinomectin were carried out in female Crl:CD-1 (ICR) BR mice and female Crl:CD (SD) rats via gavage and after intraperitoneal administration.

At doses of 19.5 mg/kg bw and higher, clinical signs included ataxia, tremor and bradypnoea. Mortality was observed at 39 mg/kg bw and higher. This is the only toxicity study with intraperitoneal administration. The NOEL in both mice and rats was 9.8 mg/kg bw. An acute oral toxicity study was carried out with Sprague-Dawley rats. The NOEL of this study was 8 mg/kg bw, based on a decreased foot splay at 10 mg/kg bw.

Repeat dose toxicity

Eprinomectin was tested via the diet in rats (two studies over 4 weeks, and one over 14 weeks) and dogs (6, 14 and 53 weeks).

Two non-GLP 4 week oral repeat dose toxicity studies were conducted in rats. Eprinomectin was administered at dose levels of 0.5, 2.5, 5, 10, 20, 30, 40 and 60 mg/kg bw per day. At the two highest doses, ataxia, hunched appearance, decreased activity, tail tremor, piloerection and whole body tremor were observed. At 30 mg/kg bw per day, the symptoms were similar but milder. Decreased body weight gain was observed at 20 mg/kg bw per day. No effects were observed at lower doses. The dose of 10 mg/kg was retained as the NOEL.

In a 14 week oral repeat dose toxicity study in rats, eprinomectin was administered at dose levels of 0, 1, 5 and 20 mg/kg bw per day. Animals treated with the highest dose showed mydriasis, ataxia and salivation and degeneration of the sciatic nerves. A NOEL of 5 mg/kg bw per day was retained for this study.

Dogs were treated with eprinomectin for 6 and 14 weeks at dose levels between 0.5 and 4 mg/kg bw per day. Ataxia, salivation and mydriasis were consistently seen at 1.6 mg/kg bw per day and above. A NOEL of 0.8 mg/kg bw per day was retained.

In a 53 week oral repeat dose toxicity study in dogs, eprinomectin was administered via their diet for 0, 0.4, 1 and 2 mg/kg bw per day. Mydriasis occurred at the top dose. Histopathological examinations showed pons and/or cerebellar nuclei indicating slight focal degeneration. A NOEL of 1 mg/kg bw per day was retained for this study.

The adverse effects on the central nervous system were consistent between studies. These effects are probably due to the pharmacological activity. Dogs were the most sensitive species with a NOEL of 0.8 mg/kg bw/day in the 14-week study and 1 mg/kg bw/day in the 53 week study.

Tolerance in the target species of animal

See part 4.

Reproductive toxicity

Study of the effect on reproduction

In a non-GLP one generation dose range finding study for reproduction toxicity with rats, the dietary concentration of eprinomectin was 0, 7, 36, 181 mg/kg feed before mating, during pregnancy and lactation. Reduced body weight gain was observed in adults and pups at the two highest dose levels. At the top level, reproductive performance was reduced. Body tremors were observed in the litters at dietary concentrations of 36 and 181 mg/kg feed.

A two generation reproductive toxicity study was conducted in rats, with one litter each for the first and two litters each for the second generation. Eprinomectin was given via the diet at equivalent doses of 0, 1, 2.8 and 6 mg/kg bw per day before mating, during pregnancy and lactation. Reduced reproductive performance was observed in adults at the highest dose level. Body tremors were observed in the litter at 2.8 and 6 mg/kg bw per day. The latter concentration increased pup mortality, decreased litter weight and pup growth. From this study a NOEL of 1 mg/kg bw/day was established.

A further study showed that the milk to plasma ratio of eprinomectin was 3:1, resulting in enhanced neonatal exposure in nursing pups.

For reproductive safety of the product in the target species, cattle, see part 4.

Study of developmental toxicity

Developmental toxicity was investigated in rats and rabbits.

Rats receiving equivalent doses ranging from 0.4 to 14 mg/kg bw/day of eprinomectin showed no adverse effects for dosages up to 1 mg/kg bw/day in dams and no adverse effects for doses up to 14 mg/kg bw/day in pups. No teratogenic effect was observed.

Three studies were conducted in rabbits. Eprinomectin was administered by gavage at doses between 0.5 and 8 mg/kg bw/day. Mydriasis and slowed pupillary reflexes were observed consistently at 2 mg/kg bw/day and above. The NOEL of eprinomectin in rabbits for maternal toxicity was 1.2 mg/kg bw/day. No evidence of foetotoxicity or teratogenicity was noted up to 8 mg/kg bw/day.

Based on the above described rat and rabbit studies, eprinomectin showed no potential for teratogenicity.

Genotoxicity

A set of mutagenicity tests (Ames test, *in vitro* gene mutation test with V79 Chinese hamster lung cells at the HPRT locus, *in vitro* chromosomal aberration test (CHO cells) and *in vivo* micronucleus assay in mice) was conducted. No mutagenic activity was observed. In addition, eprinomectin gave negative results in the i*n vitro* alkaline elution/primary rat hepatocyte assay measuring DNA strand breaks.

Based on the above described studies, eprinomectin showed no mutagenic potential in a set of mutagenicity tests.

Carcinogenicity

Carcinogenicity studies have not been conducted with eprinomectin. This is considered justified based on the negative results of the genotoxicity studies and the absence of any findings suggestive of carcinogenic potential in the repeated dose toxicity studies. Eprinomectin has no structural relationship to known carcinogens and in addition closely related compounds showed no carcinogenic potential in long term studies in rats and mice.

Studies of other effects

Neurotoxic potential of eprinomectin was evaluated in an acute toxicity study in rats including a functional observational battery. Eprinomectin was administered via gavage once at dose levels of 0, 8, 10, 13, 20 and 25 mg/kg bw per day. Animals treated with 13 mg/kg bw and above showed salivation, hypoactivity, tremors and hunched posture and a decreased foot splay was seen at 10 mg/kg bw. A NOEL of 8 mg/kg bw was retained for this study. The substance was found to be neurotoxic.

No specific studies on immunotoxicity were provided. This is acceptable because no indications of such effects were observed in the toxicology or pharmacodynamic studies. Therefore, the absence of any specific studies was justified.

Human data

Eprinomectin is exclusively approved for use as veterinary drug, thus no human data following the administration of eprinomectin are available.

Excipients

Excipients in the product include the following: N-methyl pyrrolidone (NMP), poly (lactic-*co*-glycolic) acid (PLGA); butylhydroxytoluene (BHT) and triacetinIn addition, eprinomectin contains Vitamin E.

NMP is included in Table 1, Allowed Substances, of the Annex to Regulation (EU) No 37/2010, as shown below. However, it is has been classified by the European Chemicals Agency (ECHA) as being a "substance of very high concern" due to the potential of this substance to "damage fertility or the unborn child". No information regarding the toxicity studies on which the classification was based was available. Literature studies provided toxicity data for NMP: the oral NOEL is 125 mg/kg bw per day (decreased foetal weight was observed at 250 mg/kg bw per day) based on an oral developmental toxicity study in SD rats, which were treated on gestation days 6 through 20 with 125, 250, 500 and 750 mg/kg bw per day. The reproductive toxicity findings were inconsistent regarding dose level and effects. The lowest NOEL regarding male fertility was 50 mg/kg bw per day (effects on the testis in the F1 generation of a 2-generation study with rats), however, other 2-generation studies did not reproduce these findings. Testicular lesions, atrophy or smaller testicles were also observed in several repeated dose studies with NOAELs ranging from 207 mg/kg bw per day (2-year study in rats) to 1033 mg/kg bw per day (28-day subchronic study in rats).

BHT is an approved food additive (E321) as is triacetin (glyceryl triacetate; E1518) and as such, both are covered by an entry in Table 1 of the Annex to Regulation (EU) No 37/2010 (substances with a valid E number approved as additives in foodstuffs for human consumption).

PLGA is included in the Out of scope list (EMA/CVMP/519714/2009-Rev.35). It is a polymer consisting of lactic acid, which is an endogenous substance in the human body, and glycolic acid, which is part of the natural human diet. PLGA undergoes hydrolysis in the body to produce the original monomers, lactic acid and glycolic acid. PLGA is already used in medicinal products for human use, as an excipient for the prolonged release of active substance after subcutaneous injection.

Vitamin E can be found naturally in some foods. The expected dose is well below the recommended daily intake of Vitamin E.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/543/03-Rev.1.

The user is a person with the skills to administer the product (veterinarian, farmer). Exposure to children is considered to be negligible due to the product's use, storage indications, packaging, route and method of administration.

The main potential routes of accidental contact with the product are those of dermal or eye exposure and accidental self-injection.

Acute toxicity studies with the product were not performed.

No skin irritating and no sensitizing effects were observed in animals after treatment with the product. Risk mitigating measures include warnings to avoid contact with eyes and skin and to rinse eyes and skin if exposure occurs. However, a user warning to avoid contact with the product in case of a known hypersensitivity to ingredients is required.

In the quantitative risk assessment acute and chronic exposure resulting from accidental self-injection were considered by the applicant, taking into account the slow release of eprinomectin from the PLGA.

Accidental self-injection of 1 ml of the product would correspond to an eprinomectin dose of 0.8 mg/kg bw. The available toxicological reference values for eprinomectin with which to compare this exposure would be 8 mg/kg bw from an acute neurotoxicity study in rats and 1 mg/kg bw per day from the 53-week oral gavage toxicity study in beagle dogs. Assuming that the entire amount would be systemically available directly after accidental self-injection, a margin of safety of 10 was calculated. However, due to the formulation of the product, this can be considered unlikely. Nevertheless, a safety warning to immediately seek medical advice after accidental-injection is included as risk mitigating measure. As the PLGA takes 120 days to dissolve, the exposure dose can be divided by 120 for the chronic exposure scenario. This provides a Margin of Safety of 111, which is considered acceptable.

The available toxicological reference value with which to compare the NMP dose after accidental self-injection is 125 mg/kg bw per day, based on an oral developmental study in SD rats, which were treated on gestation days 6 through 20. Assuming that the entire amount would be systemically available directly after accidental self-injection, a margin of safety of 25 was calculated. As the toxicological reference value is derived from a study that was only 15 days long, a warning that women intending to become pregnant, those who are pregnant and those that are breastfeeding should exercise caution to avoid accidental self-injection was included in the SPC. However, this RMM should be amended in the SPC, insofar as the handling of the product should be avoided altogether by this group if authorised. NMP is released rather rapidly from the PLGA matrix, and NMP levels in plasma were below quantification after 56 days. Thus, a chronic long-term exposure over 120 days is unlikely. Assuming a continuous exposure of 56 days, the MOE is 1404, which is considered acceptable.

The reproductive toxicity findings of NMP were inconsistent regarding dose level and effects. The lowest NOEL regarding male fertility was 50 mg/kg bw per day, however, other studies could not reproduce these findings. Considering this toxicological reference value, the acute margin of safety would be just 10. However, the NOEL is based on chronic long-term exposure. The application of a more relevant NOEL of 1033 mg/kg bw (LOEL: testis degeneration/atrophy at 1234 mg/kg bw) from a 28-day sub-chronic study results in a MOE of 207, which is considered acceptable.

Environmental risk assessment

A Phase I and Phase II environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines (VICH guidelines GL6 and GL38 and CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

Phase I

The predicted environmental concentrations (PECs) for soil (PECsoil-initial) were calculated to be 4.18 µg/kg for pasture animals (beef cattle) and 5.83 µg/kg for intensively reared animals (cattle >2 years). According to the Phase I ERA, a Phase II ERA is required for products that are endo- and ectoparasiticides for cattle reared on pasture, irrespective from the PEC soil. Hence, a Phase II ERA was also conducted.

Phase II Tier A

PEC values were calculated for surface water, soil, groundwater and dung in accordance with VICH guideline GL6 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1). PEC values for pasture animals were refined taking into

account distribution water/sediment and excretion data taken from PEC refinement for intensively reared animals was performed with FOCUS surface water modelling.

Exposure assessment	Pasture (direct exposure)	Intensively reared
	Value (µg/l – µg/kg)	
PEC soil initial	4.18 µg/kg_{dwt}	5.83 µg/kg_{dwt} (cattle >2 years)
PEC groundwater	<0.0 µg/l	<0.0 µg/l
PEC surface water refined	0.00143 µg/l*	0.0165 µg/l (cattle > 2 years)** 0.0060 µg/l (cattle 0-1 year)**
PEC sediment refined	3.10 µg/kg_{dwt}*	1.061 µg/kgdwt (cattle > 2 years)** 0.386 µg/kgdwt (cattle 0-1 year)**
PEC dung (84% moisture)	4150 µg/kg_{dwt}	-/-

* based on partitioning between water and sediment & excretion data

** refined with FOCUS_Surface Water

The n-octanol/water coefficient logPow is higher than 4, indicating a potential for bioaccumulation. Hence, the bioaccumulation assessment was performed in Phase II Tier B.

The study on transformation in water/sediment (OECD 308) systems showed significant partitioning of eprinomectin into sediment, and assessment of the toxicity to sediment dwelling organisms was performed in Phase II Tier B (OECD 218). Eprinomectin was shown to be very persistent in water and sediment (OECD 308). Eprinomectin is also persistent in soils according to the results of the study on transformation in soils presented (OECD 307).

The data on toxicity to terrestrial plants and soil microorganisms were not considered in the risk characterisation as the trigger value as per the guideline in Phase I was not exceeded. Additionally, the toxicity to other non-target arthropods was addressed by data read-across of structurally similar compounds for deriving a weight-of-evidence eprinomectin PNEC value for Collembola. Based on the most sensitive NOECs for abamectin and ivermectin with *Folsomia candida* and *Folsomia fementaria*, respectively, compared with the PECsoil refined for eprinomectin, the RQ would be below 1, indicating no risk.

The Tier A risk characterisation indicated a risk (RQ ≥1) for the aquatic compartment based on the PNEC for *Daphnia magna* (OECD 202, acute immobilisation test), and further assessment was performed in Phase II Tier B.

A risk was also indicated for the dung compartment based on the PNEC determined in the test on developmental toxicity to the dipteran dung fly *Scatophaga stercoraria* (OECD 228) as well as for dung beetles (*Ontophagus taurus*, OECD guidance No. 122).

For further assessment of the risk to dung fauna a field study was provided with two distinct pour-on applications of 0.5 mg eprinomectin/kg bw. The field study was not considered acceptable for the evaluation of the effects of LONGRANGE on dung fauna, since the excretion profile of eprinomectin applied as pour on is not comparable to the excretion profile seen in three studies with LONGRANGE Prolonged Release solution for injection. Additionally, the field study cannot be considered as representative for Europe including various geographic and climatic regions as it was conducted in a southern part of one European country only. Further main shortcomings are the lack of control with manure spiked with VMP to a level corresponding to the highest EC50 value in Tier A, collection of dung pats were done already after 48 hours and their degradation was not monitored. Therefore, the relevance of the results of this study is considered questionable. In order to control the risk identified for dung fauna in the Phase II Tier A ERA, the MAH proposed as a mitigation measure to leave 20% of the

herd untreated. This would allow for the creation of *refugia* (i.e., a number of dung pats in which dung fauna could survive and reproduce during the period of unfavourable conditions from the dung pats from treated animals), that would allow for the maintenance of the dung fauna population.

This risk mitigation measure (RMM), i.e. to leave part of the herd untreated, was established based on the potential long-term impact on dung fauna as predicted in a matrix modelling approach (using Monte-Carlo simulations), using the yellow dung fly (*Scathophaga stercoraria*) population as a model species. The model results show that the probability for population survival of yellow dung flies is higher when a higher proportion of the herd remains untreated. This modelling approach shows promising results in relation to the use of targeted treatment as a suitable measure to reduce the long-term impact on dung fauna from the use of parasiticides in pasture animals. However, the results of the model, as presented, are subject to several crucial uncertainties. First of all, the model has not been validated with field data, especially for the main parameter 'adult survival rate' which is the main driver of natural variability. In some cases the model parameters can be considered a 'worst-case assumption'; yet some external parameters have not been considered. Variations of these parameters and their indirect effects may play major roles, especially in cases where the population is already close to extinction. Finally, the conclusion from the modelling results showing that limiting treatment to 80 % of the herd will prevent dung fly populations from extinction is highly uncertain, given that in this treatment scenario the modelling results show that the population survives in 57 % of the simulated cases, yet in 43% of the cases the population goes extinct.

Based on the modelling results, and considering the conclusions on the persistence of LONGRANGE in soil and cattle manure (with DT50s in manure of 312-3922 days) (OECD 307, and EMA/CVMP/ERA/430327/2009), it is not possible to conclude with a sufficient degree of certainty that leaving 20% of the herd untreated is an effective RMM to protect against the long-term effects on dung fauna from the use of LONGRANGE in pasture cattle (i.e., by providing a sufficient number of dung pats with favourable conditions for survival and reproduction of dung species).

Phase II Tier B

For further assessment of the risk to aquatic organisms, a study on *Daphnia magna* reproduction in accordance with OECD guideline 211 was provided. Based on the results of this study, a risk to aquatic organisms was not indicated.

A study on toxicity to sediment dwelling organisms was provided (OECD 218). Based on the results, a risk was indicated for the sediment compartment for both pasture and intensively reared animals. In order to establish appropriate risk mitigation measures, PEC sediment refinements and re-calculation of the respective risk quotients were performed. Based on these results, a risk could not be excluded from the use of the product in intensively reared animals. Therefore, the use of LONGRANGE has to be restricted to pasture animals only and a respective warning sentence was proposed to be included in the SPC section 4.5: *"Not for use in animals that are reared indoors".* For the scenario 'pasture animals', the risk for the sediment compartment could be mitigated when access of cattle to water bodies is restricted for three weeks after treatment. The following risk mitigation measure was proposed to be included in the SPC section 4.5: *"The risk to aquatic ecosystems will be reduced by keeping treated cattle away from lakes and streams for three weeks after treatment".*

A bioconcentration study in fish in accordance with OECD guideline 305 was provided concluding that eprinomectin is not bioaccumulative.

Substance (eprinomectin):			
Phase II, Tier A Physical-chemical properties and fate			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	3.5 mg/l at pH 7.26 and 25 °C	plausible
Dissociation constants in water pKa	OECD 112	Not determined	plausible
UV-Visible Absorption Spectrum	OECD 101	244 nm	plausible
Melting Point/Melting Range	OECD 102	163 – 166 °C	plausible
Vapour Pressure	OECD 104	5.3E-4 Pa	plausible
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 123	logP_{ow}=5.51 at pH 4 logP_{ow}=5.61 at pH 7 logP_{ow}=5.56 at pH 9 at 25 °C	valid, plausible
Soil Adsorption/Desorption	OECD 106	Kd Koc pH %o.c. soil 21.4 2750 7.1 0.75 silt loam 15.7 1000 8.2 1.57 silt loam 6.4 4790 6.1 0.11 sandy loam 88.2 3231 7.8 2.73 loam 53.1 4962 6.3 1.07 sandy loam 133.5 9208 7.7 1.45 clay loam (Kd and Koc in L/kg)	valid, plausible
Aerobic Transformation in Soil	OECD 307	$DT_{50\ soil\ 1;\ 20°C/12°C}$ =10.9/23.3 d $DT_{50\ soil\ 2;\ 20°C/12°C}$ =13.2/28.2 d $DT_{50\ soil\ 3;\ 20°C/12°C}$ = 67.0/**143 d** $DT_{50\ soil\ 3;\ 20°C/12°C}$ = 62.4/133.2 d At 20 °C/ 12 °C Transformation products (TP) > 10%: 5 TPs from which 3 TPs increased until the end of test, % Mineralisation not measured % NER* 4.9-11.9% at day 120	Acceptable Information on soils Soil 1:DU (sandy clay loam); Soil 2, MSL (sandy loam); Soil 3, PD (loamy sand); Soil 4, RMN (loamy sand) Eprinomectin and 3 TPs are persistent in soil

Substance (eprinomectin):			
Phase II, Tier A Physical-chemical properties and fate			
Study type	**Test protocol**	**Result**	**Remarks**
Transformation in Cattle Manure	CVMP GL on the fate of VMPs in cattle manure (EMEA/CVMP/ERA/430327/2009)	DT50 at study /relevant temperature $DT_{50\ manure1;\ 20°C/10°C}$ =312/805 d $DT_{50\ manure2;\ 20°C/10°C}$ =905/2335 d $DT_{50\ manure3;\ 20°C/10°C}$ =1520/3922 **d** $DT_{50\ manure4;\ 20°C/10°C}$ = 1060/2735 d $DT_{50\ manure5;\ 20°C/10°C}$ = 669/1726 d Transformation products > 10% no 85.3-88.1%% parent at 91 d day ½ default storage time	Acceptable Temperature (at which study was conducted): 20 °C
Aerobic Transformation in Aquatic Sediment Systems	OECD 308	System 1: Taunton river (high organic matter) Corrected to 12 °C Kinetic model = SFO DT50, water =23.5 d DT50, sediment = stable DT50, total system =399 d NER* day100 = 10% Transformation products > 10%: System 2: Weweantic river (low organic matter) Corrected to 12 °C Kinetic model = SFO DT50, water =44.8 days DT50, sediment = stable DT50, total system =219.8 days Transformation products > 10%: NER* day100 = 12.1%	Acceptable Temperature(at which study was conducted): 20 °C Eprinomectin is persistent in water, very persistent in sediment systems
Photolysis	OECD 316	not degrade by a direct photolytic process	
Hydrolysis	OECD 111	DT50 = 14 d at pH 4 DT50 = 222 d at pH 7 DT50 = 73 d at pH 9 at 25 °C	

* NER = Non extractable residues

Phase II Tier A Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks**
Algae, Growth Inhibition *Pseudokirchneriella subcapita*	OECD 201	EC50	3400	µg/l	Valid, plausible
Daphnia magna, immobilisation	OECD 202	EC50	0.45	µg/l	Valid, plausible
Fish, acute toxicity/ FDA TDA 4.11/ *Lepomis macrochyrus*	OECD 203	LC50	370	µg/l	Valid, plausible
Nitrogen Transformation (28d)	OECD 216	-/-	-/-		n.d. Acceptable
Earthworm, reproduction Eisenia fetida	OECD 222	NOEC	19	mg/kg	
Terrestrial plants, seed germination & root elongation	FDA 4.06	NOEC	8.5	mg/kg	Lactuca sativa, Lolium perenne, Lycopersicon esculentum & Tritium aestivum
Terrestrial plants, seedling growth	FDA 4.07	NOEC	0.47	mg/kg	Cucumis sativus, Lolium perenne, Lycopersicon esculentum & Triticum aestivum
Dung fly larvae, Development toxicity *Scatophaga stercoraria*	OECD 228	EC50	216	$\mu g/kg_{dwt}$ [1]	Valid, plausible
Dung beetle larvae, Development toxicity *Ontophagus taurus*	Guidance document No.122	EC50	759	$\mu g/kg_{dwt}$	Valid, plausible
Phase II, Tier B studies					
Bioaccumulation in fish/*species*	OECD 305	BMF lipid, growth corrected	0.0303		lipid correction factor 1.003; not B
Daphnia magna, Reproduction	OECD 211	NOEC	0.028	µg/l	Valid, plausible
Sediment dwelling organism/*Chironomus riparius*	OECD 218	NOEC	0.34	$\mu g/kg_{dwt}$	Valid, plausible

Footnote: [1] Dung weight

Phase II Tier A/B PBT hazard assessment

Substance (INN/Invented Name): eprinomectin			
CAS-number (if available): 133305-88-1, 133305-89-2			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 123	$logP_{ow}$=5.51 at pH 4 $logP_{ow}$=5.61 at pH 7 $logP_{ow}$=5.56 at pH 9	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**	**Result**	**Conclusion**
Bioaccumulation	BMF lipid, growth corrected	0.0303	**not B**
Persistence	OECD 307 DT_{50} in soil	$DT_{50\ soil\ 3;\ 20°C/12°C}$ = 67.0/143 d Transformation products (TP) > 10%: 5 TPs, Met4, 5, and 7 were still increasing till end of test	**P** Eprinomectin and three TPs (Met4, 5, 7) are persistent in soil
	OECD 308 $DT_{50\ water}$ $DT_{50\ sediment}$ $DT_{50\ total\ system}$	$DT_{50,\ water;\ 12°C}$ =23.5 /44.8 d $DT_{50,\ sediment,\ 12°C}$ =stable /stable $DT_{50,\ total\ system,\ 12°C}$ =399 / 219.8 d	**P** in water, **vP** in sediment
Toxicity	NOEC (*Daphnia magna* reproduction)	0.028 µg/l	**T**
PBT-statement :	The compound is considered as P and T.		

Conclusions on the environmental risk assessment

Based on the provided data, no risk is indicated for the aquatic compartment. The risk to the sediment compartment can be mitigated by the following risk mitigation measure and warning sentence to be included in the SPC section 4.5 if authorised:

'*Eprinomectin is very toxic to dung fauna and some aquatic organisms and may accumulate in sediments.*

The risk to aquatic ecosystems will be reduced by keeping treated cattle away from lakes and streams for three weeks after treatment.

Not for use in animals that are reared indoors.'

However, the presented data indicate a serious risk to dung fauna lasting over and most likely beyond the entire period of persistent antiparasitic activity of this product and there is no appropriate risk mitigation measures in line with agricultural practices available to mitigate this risk to an acceptable level. Indeed according to the model approach provided by the applicant, at 80% of herd treated and 20% untreated the dung fly population would go extinct completely in a considerable number of

simulated cases. Therefore, it is not possible to conclude with a sufficient degree of certainty whether the risk mitigation measure to leave 20% of herd untreated is sufficiently protective and hence, it is considered not acceptable. Additionally, it has to be considered that given the very persistent nature of this substance in soil and dung pats a long-term exposure to dung fauna is very likely.

Residues documentation

The ingredient PLGA changes the absorption behaviour of eprinomectin as it forms a hydrophobic polymeric gel matrix after injection. Eprinomectin is embedded in the polymer and slowly released resulting in a prolonged absorption from the injection site.

Specific absorption behaviour as well as high residue concentrations at injection sites made specific adjustments to the site of administration and the conduct of residue depletion studies for edible tissues necessary.

Pharmacokinetics

Study data consistently show prolonged and biphasic depletion of eprinomectin from plasma. According to the pivotal pharmacokinetic study (see part 4), the average maximum concentration of 26.0±8.47 ng/ml was reached 1–3 days after treatment, followed by a continued gradual release of eprinomectin. Eprinomectin plasma concentrations increased slightly again between days 70 and 91, and then decreased until days 105–154. Available data indicate differences in pharmacokinetic profiles between shoulder versus ear injection and between lactating dairy versus young beef cattle when administered at the base of the ear.

Faeces are the major route of excretion of eprinomectin in cattle. Eprinomectin is not extensively metabolised in cattle, as the parent drug was the main residue at all slaughter times in all tissues (90–95%), plasma (95%), and faeces (86%). The compound eprinomectin B1a was also the major constituent accounting for 80–85.6% of the total extractable radioactivity in milk. The metabolic profile of eprinomectin after application via subcutaneous injection was shown to be similar to that after topical administration.

Data from a study using ^{3}H labelled eprinomectin and ^{14}C labelled N-methyl pyrrolidone via subcutaneous injection at the shoulder showed that eprinomectin B1a was the only major ^{3}H-residue. ^{14}C-N-methyl pyrrolidone depletes rapidly from tissues, with levels at injection sites similar to or lower than in other muscle samples. After Day 56, the ^{14}C-NMP levels in all plasma samples were not quantifiable.

Residue studies

Residue concentrations at (normal) injection sites were shown to be highly variable and showed much higher concentrations than in the other edible tissues, which would lead to very long withdrawal periods if injection site tissue would be taken into account in the assessment of consumer safety. Ear is considered not to be an edible tissue and was therefore chosen as injection site. Samples from tongue and cheek muscle as well as fat tissue behind the ear were considered appropriate to monitor residue concentrations in tissues around the injection site.

Depletion of residues

Tissues

One pivotal GLP-compliant tissue residue depletion study for the target species cattle (male and female

animals, 250-369 kg bw) was designed as marker residue study to determine eprinomectin B1a concentrations in liver, kidney, peri-renal fat, right loin muscle, tongue, right cheek muscle and fat behind the ear near the injection site of the target animals and to derive withdrawal periods. The target animals were treated with the commercial formulation at the intended dose of 1 mg eprinomectin per kg bw by subcutaneous injection at the back of the right ear. A sufficient number of animals (six per group) and slaughter time points (ten) were investigated.

Residue concentrations were determined in tissues between day 21 and 210 post dose at a validated HPLC method.

Highest residue concentrations were measured in liver tissues, followed by kidney, peri-renal fat, fat behind the right ear, tongue, right cheek muscle and loin muscle. The eprinomectin B1a concentrations in loin muscle decreased to below the LOQ on Day 42, except for two quantifiable values on Day 84. The eprinomectin residues in the tongue and the right cheek muscle were also very low and decreased to below the LOQ on Day 105, except in the tongue from one animal. Residues in fat from behind the right ear were below the LOQ by Day 126 with two exceptions. Residue concentrations in loin muscle, tongue, right cheek muscle, and fat behind the right ear were all well below their corresponding MRLs. In liver, kidney, and fat tissues, residues depleted slowly from day 21 to day 63, then slightly increased from day 63 to day 84, followed by a continuous decrease until day 210.

Milk

Two residue depletion studies in milk from treated dairy cows were provided, an exploratory study and the definitive study.

The initial milk residue depletion study was conducted in six cows (584-734 kg bw) with different milk yields, treated once at the intended dose of 1 mg eprinomectin per kg bw equally divided and injected at the back of the right and left ear. Milk samples were collected from all animals on Days -1, 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 14, 21, 28, 35, 42, 49 and 56 (two milkings per day each), and assayed for the marker residue using a validated HPLC method (LOQ: 2.3 µg/l).

The highest mean milk eprinomectin concentration was determined in day 1 (PM) milk samples (11.8±1.87 µg/l), and then declined, falling below 5 µg/l on day 5, and below 2 µg/l at day 42 and after. The eprinomectin milk concentrations are well below 20 µg/l at all time-points of the study, including at the peak levels observed on days 1–2. As measurement was continued until day 56 only, a second peak is not shown in milk residue data.

The pivotal GLP-compliant residue depletion study in milk was conducted in a sufficient number of animals (20 dairy cows with different milk yield, 453-698 kg bw). The target animals were treated with the commercial formulation at the intended dose of 1 mg eprinomectin per kg bw by subcutaneous injection at the back of the ear. For dose volumes exceeding 10 ml, the total dose was distributed into two injections.

Milk samples were collected on days -1, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 28, 35 and 42 (two milkings per day, AM and PM each). On Day 0, all animals were additionally milked and sampled at 6 hours post treatment. The milk eprinomectin B1a concentration was analysed using a validated HPLC method (LOQ: 2.3 µg/l).

The highest mean milk eprinomectin B1a concentration was determined on day 1 post application (10.1±3.20 µg/l), followed by a decrease. Quantifiable levels (2.41–2.61 µg/l) of eprinomectin B1a were observed in three out of 20 animals on Day 42 PM., all other animals had eprinomectin B1a levels below limit of quantitation.

Measurements were done until day 42, i.e. it is not shown whether the increase seen in plasma

concentrations around day 70 in beef cattle would also be measurable in milk samples at later time points.

Analytical method

For the analysis of eprinomectin B1a concentrations in bovine tissues a validated HPLC fluorescence method with pre-column derivatisation was provided. A validated HPLC fluorescence method with pre-column derivatisation utilizing an internal standard was provided for eprinomectin B1a analysis in bovine milk. Performance criteria were mainly in compliance with guideline VICH 49. Individual data to allow for a recalculation of the results were available.

MRLs

The MRL status of the constituents of LONGRANGE is as follows:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions	Therapeutic classification
Eprinomectin	Eprinomectin B1a	All ruminants	50 µg/kg 250 µg/kg 1500 µg/kg 300 µg/kg 20 µg/kg	Muscle Fat Liver Kidney Milk	NO ENTRY	Antiparasitic agents / Agents against endo- and ectoparasites

The excipients listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Withdrawal periods

Tissues

According to the biphasic residue depletion profile of LONGRANGE in cattle tissues, only data from the terminal linear regression of residue depletion are relevant for calculation of withdrawal periods.

Liver is the withdrawal period determining tissue. Values measured between days 81-210 post dose were included in regression analysis according to the CVMP guideline Approach Towards Harmonization of Withdrawal Periods (EMEA/CVMP/036/95) using the programme WT1.4.

As normality (Shapiro-Wilk's test, $p<0.01$) and homogeneity of variances (Cochran- and Bartlett-test, $p<0.01$) did not pass the statistical assumption criteria, the standard approach based on regression analysis was considered as not appropriate to deal with the present residue data due to the special kinetics of this product.

95/95 tolerance limits for measured values per slaughter day was considered as the most valid approach. Calculations based on concentrations corrected for recovery of eprinomectin in liver tissues (94.3 %) result in 95/95 tolerance limits values of 2577, 1545, and 454 µg/kg at days 84, 105 and 126, respectively. As the concentrations corrected for recovery of eprinomectin in liver tissues at day 105 is slightly above the MRL, linear interpolation was used, resulting in a withdrawal period of 106 days for edible tissues from treated cattle.

Milk

As all eprinomectin residue concentrations found in milk in this study were below the MRL at all

sampling times, the Time To Safe Concentration (TTSC) method could not be used. Therefore, the Safe Concentration Per Milking (SCPM) calculation method based on Guideline EMEA/CVMP/473/98-FINAL was used for a statistical approach to the calculation of the tolerance limits for the individual milkings. The recovery corrected milk concentration data for the times of 6 hours post-dosing to 14.5 days post-dosing were used only, as data from later time points would not affect the SCPM calculations. The results of the Safe Concentration Per Milking (SCPM) calculation method would give a withdrawal period of 48 hours for eprinomectin in milk from animals treated at the intended dose of 1 mg eprinomectin per kg bw (1 ml LONGRANGE/50 kg bw) via subcutaneous injection at the back of the ear.

However, as lactating animals were removed from the product literature, withdrawal periods in milk are not applicable. The following sentence needs to be added in section 4.11 of the SPC if authorised: “Not authorised for use in animals producing milk for human consumption.”

Overall conclusions on the safety and residues documentation

Following oral administration to laboratory animals, residue levels in tissue were the highest in liver, fat, kidneys and muscle, but were also detected in plasma and red blood cells. Overall, residue levels were comparable in male and female rats. The active substance was primarily excreted via faeces.

In acute toxicity studies, the oral and intraperitoneal limit dose for neurotoxic effects is greater than 8 mg/kg bw in rats and mice. In repeat dose toxicity studies, the NOEL was 0.8 mg/kg bw/day and 1 mg/kg bw/day in a 14-week study and a 53-week study by gavage in dogs, respectively. Neurotoxicity was observed at higher dose levels. The CNS system was the main target of eprinomectin in rats, dogs and rabbits.

Data in rats and rabbits indicate that eprinomectin is not a selective developmental or reproductive toxicant.

Eprinomectin is not genotoxic. Carcinogenicity studies have not been performed and are not requested.

The product was shown to be non-irritant to skin, a non-sensitizer of skin, but a severe ocular irritant.

The data presented are considered adequate to characterise the toxicity profile of the active substance.

The most relevant routes of accidental contact are self-injection as well as dermal and eye exposure. To mitigate the risk for eye irritation, safety warning phrases to rinse hand and eyes when exposed are applied. However, a user warning to avoid contact with the product in case of a known hypersensitivity to ingredients needs to be included in part 4.5 of the SPC. An acute risk regarding neurotoxicity of eprinomectin and developmental toxicity of NMP might arise, if the entire amount of these substances were to be systemically available directly after accidental self-injection. The risk arising from accidental injection is acceptable when a prolonged release of the active substance and NMP over a period of 120 and 56 days is assumed, respectively. However, a safety warning to immediately seek medical advice after accidental-injection is included as risk mitigating measure. The warning that women intending to become pregnant, those who are pregnant and those that are breastfeeding should exercise caution to avoid accidental self-injection needs to be included in the SPC, insofar as the handling of the product should be avoided altogether by this group of users.

LONGRANGE can pose a risk to dung and sediment organisms.

The risk to the sediment compartment can be mitigated by an appropriate risk mitigation measure and warning sentence in the SPC section 4.5.

However, the presented data indicate a serious risk to dung fauna lasting over and most likely beyond the entire period of persistent antiparasitic activity of this product and there are no appropriate risk mitigation measures in line with agricultural practices available to mitigate this risk to an acceptable level. The ingredient PLGA changes the absorption behaviour of eprinomectin, resulting in a prolonged absorption from the injection site.

Plasma profiles of eprinomectin B1a show an initial maximum concentration 1–3 days after treatment followed by a continued gradual release, a second maximum concentration between days 70 and 91 and final decrease until days 105–154. The metabolism profile of eprinomectin after application of a subcutaneous injection is similar to that which occurs after topical administration. Eprinomectin is metabolised to a small extent only and eprinomectin B1a is the relevant marker residue. Faeces were shown to be the major route of excretion of eprinomectin in cattle.

Residue depletion data in cattle tissues were provided, with samples from tongue and cheek muscle, as well as fat tissue behind the ear, to account for residue concentrations in tissues around the injection site. Liver is considered to be the withdrawal period determining tissue. A withdrawal period of 106 days, based on 95/95 tolerance limits for recovery corrected values per slaughter day, is necessary to ensure consumer safety.

As lactating animals were removed from the product literature, if authorised the following sentence needs to be added in section 4.11: "Not authorised for use in animals producing milk for human consumption."

Part 4 – Efficacy

Pharmacodynamics

Eprinomectin is a well-known antiparasitic of the macrocyclic lactone family of endectocides, with pharmacodynamic properties typical for this group, i.e. killing activity against gastrointestinal nematodes, lungworms, warbles (parasitic stages), mange mites, lice and horn flies. Like for other avermectins, the antiparasitic effect is thought to be mediated *via* glutamate-gated chloride channels, which are present in invertebrate nerve and muscle cells. Binding leads to an increase in the permeability of the cell membrane to chloride ions causing hyperpolarization of affected cells and subsequent paralysis and death of the parasite.

The applicant described this mechanism and provided a selection of supportive literature, which is available in abundance in the public domain. This approach is considered appropriate and the information is correctly given in the relevant section (5.1) of the SPC.

Development of resistance

In Europe, reports on resistance of cattle nematodes and ectoparasites to eprinomectin are rare, although resistance to eprinomectin has been reported in other parts of the world. However, there are a few European reports on macrocyclic lactone (ML) class resistance in cattle, and cross resistance (or even side resistance) between eprinomectin and other ML's have been observed. Geurden *et al*. (2015) investigated 753 cattle on 40 farms in Germany, UK, Italy and France based on the faecal egg count reduction test (FECRT) after a single ML treatment and anthelmintic resistance against ivermectin and moxidectin occurred at a mean level of 12.5% on these European cattle farms. *Cooperia* spp. but also *Ostertagia ostertagi* was identified as being resistant particularly in Germany and the United Kingdom.

In a meta-analysis of factors associated with anthelmintic resistance in sheep (Falzon *et al*., 2014), the pooled odds ratio of two studies showed a marginally significant positive association between the use of long acting formulations and the development of anthelmintic resistance. However, the heterogeneity between the studies considered was high and the relevance of the finding for the development of resistance when using long-acting anthelmintics in sheep is, therefore, unclear.

Among other factors, the use of long-acting anthelmintic formulations has been identified as a possible risk factor for the selection of resistant nematodes (Sangster *et al*., 2018). Sub-optimal concentrations of the active substance may lead to the selection of resistant parasites as modelled by Leathwick and Luo (2017).

In line with the CVMP's Reflection paper on anthelmintic resistance (EMA/CVMP/EWP/573536/2013) such long-acting formulations of broad spectrum anthelmintics should only be reserved for targeted selective treatment in specific situations, e.g. when both the grazing season is long enough and the maintenance of refugia (i.e. the amount of susceptible helminth population in the environment) at farm level is assured. The applicant followed this approach and proposed the following advice for targeted selective treatment in section 4.4 of the SPC: "It is recommended to leave 20% of the herd untreated to limit the impact on dung fauna and to reduce the development of resistance. Before using this product, guidance on appropriate use and the maintenance of susceptible parasite populations should be sought from the prescriber". The applicant argued that this approach would allow for keeping a large amount of susceptible nematodes in refugia, thereby diluting the amount of resistant worms surviving anthelmintic treatment. The applicant also stated that LONGRANGE with its high peak and large area under the curve (AUC) would be no more likely to select for resistance compared to treatment with a conventional dewormer. However, the relationship between the AUC and the efficacy/resistance is unknown as the therapeutic concentration has not been determined. In addition, the persistent efficacy period of the product would finish a few months before the end of the grazing season, allowing some time for dilution of the potential resistant worms to occur by sensitive nematodes in refugia from untreated animals. In line with this, as recommended in the SPC the product is to be administered on a single occasion at the beginning of the grazing season, and only if the grazing period is more than 4 months.

The applicant's proposal of targeted selective treatment was in principle acknowledged by the CVMP. However, the committee did not accept the proposal to leave 20% of the animals in a herd untreated, as a rule, because this approach was primarily derived from a matrix model on dung fauna but no data demonstrating the impact on the development of resistance in cattle nematodes have been provided. Additionally, the committee felt that the decision on how many animals in a herd should be left untreated to maintain a susceptible worm population on pasture should be made by the responsible veterinarian on the farm, taking into account factors that may influence any strategy to maintain susceptible parasite populations on pasture, such as the pathogenicity of the parasite species, the herd size and pasture stocking, pasture contamination etc.

Pharmacokinetics

In general, pharmacokinetic characteristics of the active substance eprinomectin in cattle are well-known and information is available from the public domain. Eprinomectin exhibits stereoisomerism, and consists of two components B1a and B1b, with eprinomectin B1a being the main component. Eprinomectin is not extensively metabolised, it is highly bound to plasma proteins (>99%) and distributed in the body in various organs, including liver, kidneys, fat and muscle. As typical for substances of the avermectin group, clearance is slow and eprinomectin remains detectable in the body for weeks. It is excreted mainly via the faeces in a pattern mirroring the plasma levels. A very small amount is excreted via the urine. It can also pass the blood-milk-barrier.

For this long-acting formulation, the applicant provided a number of pharmacokinetic studies of eprinomectin (B1a component) following subcutaneous administration of LONGRANGE at the back of the ear, one pivotal pharmacokinetic study as well as three residue depletion studies In addition, a number of studies were provided using a different site of injection (front of the shoulder). The proposed dose of 1 ml LONGRANGE / 50 kg bw was used, corresponding to 1 mg eprinomectin / kg bw, if not otherwise indicated. In all these studies, eprinomectin in the long-acting formulation of LONGRANGE following subcutaneous injection, shows a biphasic pharmacokinetic profile: after a high initial peak, plasma levels drop over the following weeks, followed by a second peak and the final elimination phase. However, differences in the extent of the plasma levels were noted in regard to different injection sites and for different age groups of animals using the ear injection.

The pivotal pharmacokinetic study included 12 male Simmental calves (aged 6-7 months at the start of the study, 208-239 kg bw). The average maximum concentration of 26.0±8.47 ng/ml was reached 1-3 days after treatment (C_{max} at first peak), followed by a continued gradual release of eprinomectin. Eprinomectin plasma concentrations then increased slightly again (second peak) between days 70 and 91, and then decreased until days 105–154. The initial AUC_{1-42} was 470.2 d*ng/ml (315 - 748), and the AUC_{0-inf} was 992 (±114) d*ng/ml. The plasma half-life ($T_{0.5}$) was 9.04 days (6.74-17.0) (harmonic mean).

The height of the two peaks are strongly negatively correlated to each other (Pearson correlation coefficient for the log-transformed values -0.734, significance 0.0066), i.e. the higher the first peak the lower the second. However, plasma time curves vary between individuals, and some animals did not show a clear second peak. The biphasic pharmacokinetic profile of LONGRANGE after injection at the back of the ear is adequately reflected in section 5.2 of the SPC.

Results from the pivotal study were also reflected in the tissue residue study.

The analytical method used for eprinomectin was appropriately described, and the limits of detection and of quantification are adequate. However, with regard to the sampling time points, a higher sampling frequency would have been more appropriate. It is therefore likely that the true C_{max} of the second peak is considerably higher than measured. Due to the biphasic curve, the plasma half-life cannot be calculated in the usual manner, but is based on the plasma levels after the second peak. The terminal half-life of eprinomectin following subcutaneous injection at the base of the ear in cattle is approximately 10–17 days (depending on the study), indicating that eprinomectin is continuously released over a prolonged period of time (as compared to other, not long-acting formulations with t½ of approx. 2-3 days).

Both studies performed with injection at the back of the ear were generally well conducted.

In two further milk residue studies, pharmacokinetic data from adult, lactating dairy cows differ considerably from those in young beef cattle. Lactating dairy cows treated with the product via a subcutaneous injection at the base of the ear showed a high initial peak (approximately 60 ng/ml; i.e. about twice that observed in young cattle). The reason for this remains unknown. The most likely explanation is the distribution of the product in the tissue, leading to a greater surface of the gel matrix in lactating dairy cattle; hormonal influences that come with lactation could also play a role.

For adult, lactating dairy cows, plasma levels are only available until D42 and D56, respectively. This means that no data for the plasma trough levels before the second peak, around and after the second peak are available. In the absence of data demonstrating the claimed persistent efficacy and target animal safety (unknown margin of safety), lactating animals were removed from the product literature.

In heavy animals (more than 500 kg bw), two injection sites may be necessary. Larger injection volumes as well as use of two injection sites may lead to different rates of eprinomectin release from the gel matrix, and might change the pharmacokinetic behaviour of eprinomectin in target animals. This may have an impact concerning efficacy, target animal safety and/or residue depletion. Since it cannot be excluded that use of two injection sites will impact on the pharmacokinetics of the active substance, a maximum bodyweight of 500 kg should be set (corresponding to the maximum tested dose for one injection site, 10 ml). Corresponding information would need to be added in the SPC if authorised.

Data from other injection sites

Injection in front of shoulder in young cattle

LONGRANGE was initially developed for subcutaneous injection in front of the shoulder, and several studies were conducted using this site of administration and were reviewed in support of this application.

Overall, the absorption pharmacokinetics and the plasma time curves of the injection of LONGRANGE at the back of the ear (the intended site of injection) differ considerably from those following an injection of the same dose in front of the shoulder. A sound explanation for this effect has not been presented. Consequently, data demonstrating persistent efficacy presented with the administration of LONGRANGE in front of the shoulder cannot be extrapolated to the injection at the back of the ear.

Pour-on administration

The applicant also presented a study with eprinomectin data following pour on administration. Pharmacokinetic data showed that injection of LONGRANGE subcutaneously at the back of the ear resulted in a significantly higher systemic exposure (C_{max} and $AUC_{0\text{-}21\ days}$) than pour-on administration. Considering these, it can be concluded that initial peak plasma levels after LONGRANGE injection are at least equal to those obtained after pour-on application at the recommended dose.

Dose justification

The dose of 1 mg/kg bodyweight (1 ml/50 kg bw) for LONGRANGE was proposed based on the findings of a dose determination study investigating the pharmacokinetic profile of eprinomectin after a single subcutaneous dose of 0.5, 0.75 or 1 mg/kg bw at the shoulder, and efficacy against induced larval nematode infections at day 120 post-dose. The product formulation intended for marketing was not used.

However, in this study already the lowest tested dose of 0.5 mg eprinomectin/kg bw proved to be highly effective (95% or higher) against gastrointestinal nematodes (*Ostertagia ostertagi, Cooperia oncophora, Trichostrongylus axei, Haemonchus placei and Nematodirus helvetianus*), and lungworm infections (*Dictyocaulus viviparus*) induced on day 120 post-dose. Also, as evident from the pharmacokinetic studies (see above), eprinomectin plasma concentrations following a single dose of 1 mg/kg bw differ following administration at the back of the ear compared to administration in the shoulder. The selected treatment dose may therefore not be the optimum one from an efficacy perspective. Given, however, that immediate and persistent efficacy has been demonstrated after administration at the recommended dose of 1 mg/kg bw at the back of the ear for gastrointestinal nematodes and lungworms in a sufficient number of dose confirmation studies, supported by a field study, the recommended dose 1 mg/kg bw s.c. (sub cutaneous) at the back of the ear was accepted.

Dose confirmation studies

A large number of studies were presented to confirm immediate and persistent efficacy of LONGRANGE at a single dose of 1 mg/kg bw under controlled conditions (natural or induced infections) in nematodes and ectoparasites. The studies were conducted in Europe and the USA after subcutaneous administration of the test product either in the shoulder or the base of the ear.

Nematodes

(*Dictyocaulus viviparus, Ostertagia ostertagi/lyrata, Trichostrongylus colubriformis, Haemonchus contortus*, and *Bunostomum phlebotomum* for 120 days, and *Oesophagostomum radiatum, Cooperia oncophora/surnabada, C. punctata* and *Trichostrongylus axei, and Nematodirus helvetianus)*

Immediate (therapeutic) efficacy

Shoulder injection

The applicant provided 13 GCP-compliant controlled randomized blinded dose confirmation studies to demonstrate immediate (therapeutic) efficacy against artificially induced or natural nematode- and lungworm infections after s.c. administration of LONGRANGE at a single dose of 1 mg/kg bw (1 ml/50 kg bw) in the front of the shoulder. Seven studies were conducted in Europe (Germany, UK) and six studies in the USA. All studies were designed according to the recommendations of VICH GL7 and GL12

Healthy young beef cattle of different breeds (Holsteins, Braunvieh, Limousin, Fleckvieh, Angus, Swiss Brown and cross-breeds) aged 3–15 months were used.

Natural infection (shoulder injection)

Five studies were conducted to demonstrate the immediate, therapeutic efficacy of eprinomectin against natural (inhibited) larval and adult stage infections. The pivotal studies were conducted in the UK and Germany; in addition, three studies conducted in the USA were provided. Infections with nematodes were naturally acquired by cattle grazing on infected pastures for at least 4 weeks. Pasture infestation was confirmed by herbage counts, faecal egg counts and tracer calf worm counts. Approximately 14 days prior to treatment all animals were removed from pasture and held indoors under conditions designed to preclude further nematode infection for approx. 4 weeks. Animals were necropsied on day +14–15 post treatment and abomasa, small and large intestines and lungs were collected for parasite recovery and counting.

Efficacy was calculated on parasite species level according to the relevant VICH guidelines. Under these conditions, it is assumed that all nematodes with a pre-patent period of 3 to 4 weeks had adequate time to develop into adult stages and that immature nematodes recovered in L4 stages should be considered inhibited. In general, tracer calves proved to be infected with *Ostertagia* spp. inhibited L4 larvae and with gastrointestinal nematodes from the genera *Ostertagia, Haemonchus, Trichostrongylus, Cooperia, Trichuris, Oesophagostomum, Capillaria, Nematodirus,* and *Dictyocaulus* lungworms.

Induced infection (shoulder injection)

Six studies were conducted in order to demonstrate the immediate efficacy of eprinomectin against induced larval and adult stage infections of the target gastrointestinal nematode species and lungworms, respectively. Studies (larval and adult stage infections) were conducted in Germany, UK and USA. The inoculation scheme was designed so that the parasites were expected to be L4 stages and adults, respectively, at the time of treatment. The inoculation doses were in line with VICH GL7 and GL12 and generally adequate to induce appropriate infection levels in control animals. At the time the

studies were conducted, the parasite strains used for infection were recent field isolates (< 10 years old) from naturally infected cattle or sheep and maintained since then under laboratory conditions. All animals were necropsied on D+21/+22 post treatment (larval stage infections) and D+14/15 post treatment (adult stage infections), and abomasa, small and large intestines and lungs were collected for parasite recovery and counting. Efficacy was calculated on species level/developmental stages identified on morphology, and based on geometric means according to VICH GL7.

In addition, two dose confirmation (DC) studies were conducted to confirm efficacy against *B. phlebotomum* (adult, L4) after induced infection. One study was conducted in Germany, and an additional one in the USA. All animals were inoculated with L3 of *B. phlebotomum* topically into the ear canal on D-15. The larvae used for inoculation originated from recent field isolates (< 10 years old) from cattle. Nematodes were expected to be L4 stages and adults on D0 and D+42, respectively. Groups of animals were treated on D0 and D+42, respectively, and were necropsied on D+56/57 post treatment and small intestines were collected for nematode recovery and counting.

Ear injection

Two GCP-compliant randomized controlled dose confirmation studies conducted in Germany (2015) were provided using LONGRANGE at a dose of 1 mg/kg bw at the recommended route of administration, i.e. the back of the ear. Young male beef cattle were challenged with larval (L3) nematode infections. The inoculation schedule was designed so that nematodes were expected to be larval (L4) stages and adults on the day of treatment (D 0), respectively. The parasite strains used for infection were recent field isolates (< 10 years old) from naturally infected cattle or sheep from Germany and maintained since then under laboratory conditions. Animals infected with larval nematode stages were necropsied on D+21 post treatment, and animals infected with adult stages were necropsied at D+14 post treatment. Abomasa, small intestines, large intestines including caecum and the lungs were collected for parasite recovery and counting. Efficacy was calculated based on species level according to VICH guidelines.

Treatment with LONGRANGE at the recommended dose and route of administration (back of the ear at a dose of 1 mg/kg bw) proved to be 100% or nearly 100% effective against adult and larval (L4) stages of H. contortus, C. oncophora/surnabada, C. punctata, T. colubriformis, N. helvetianus, B. phlebotomum, Oes. radiatum and D. viviparus, O. ostertagi/lyrata and T. axei. The immediate (therapeutic) efficacy of LONGRANGE against gastrointestinal nematode and lung worm infections in young beef cattle was in the same magnitude following single injection (1 mg/kg bw) at the back of the ear or in the shoulder.

Conclusions (immediate efficacy)

In line with a scientific advice (EMA/CVMP/SAWP/546246/2014), CVMP accepted that in the case of immediate efficacy, results of studies using the shoulder injection can be extrapolated to LONGRANGE when administered at the back of the ear. Eprinomectin plasma levels in young beef cattle after ear injection showed a significantly higher 1st peak (p=0.0016) when compared to the injection in front of the shoulder. The 90% confidence interval for the ear-shoulder ratio of 1st peak heights was 130%-207% (point estimate 164%).

Under the conditions of these studies, LONGRANGE proved to be effective (>90%) in the treatment of gastrointestinal nematode infections (adult and inhibited larval stages (L4)) with *Ostertagia* spp. (*Ostertagia ostertagi/lyrata),*Cooperia *spp(Cooperia oncophora/ surnabada, C. punctata), Haemonchus* spp *(Haemonchus contortus), Trichostrongylus* spp. *(Trichostrongylus axei, T. colubriformis, Bunostomum phlebotomum),Nematodirus* spp *(Nematodirus helvetianus),*

Oesophagostomum radiatum, and *Dictyocaulus viviparus*. The immediate (therapeutic) efficacy of LONGRANGE against gastrointestinal nematodes and lungworms following a single injection at a dose of 1 mg/kg bw at the back of the ear in young beef cattle was confirmed in two dose confirmation studies. Efficacy was in the same magnitude (>90%) when compared to the injection of LONGRANGE into the shoulder.

Persistent efficacy: Prevention of reinfections

Induced infection (ear injection)

Two GCP compliant saline-controlled randomised dose confirmation studies were conducted in Europe to demonstrate the persistent efficacy of LONGRANGE against nematodes at a single subcutaneous dose of 1 mg/kg bw at the back of the ear for up to 100 and 120 days, respectively (Germany, UK). Healthy male and female beef cattle of different (cross-) breeds, aged approximately 4 months were used. Groups of animals received a single injection of LONGRANGE either on D0 or D+20. Each animal was then challenged daily on D+100 to 120 with infective L3 larvae of gastrointestinal nematodes and lungworms. The parasite strains used for infection were recent field isolates (< 10 years old) from naturally infected cattle or sheep from Germany and UK, respectively, and maintained since then under laboratory conditions. Animals were euthanized on D+148–150 post treatment and their lungs, abomasa, small and large intestines, including caecum, collected for parasite recovery and counting. Efficacy was calculated according to the relevant standards.

Under the conditions of these two studies, LONGRANGE proved to be effective (at least 90%) in the prevention of the establishment of infections *with O. ostertagi, B. phlebotomum* and *D. viviparus* for up to 120 days after treatment and with *C. punctata , C. oncophora/surnabada, O. radiatum* and *T. axei* for up to 100 days after treatment.

Adequate preventive efficacy against *Haemonchus contortus* and *Trichostrongylus colubriformis* for 120 days could only be demonstrated in one of the studies. Nevertheless, the committee agreed with a persistent efficacy period of up to 120 days for the blood sucking nematode *H. contortus* based on both the results of the well-controlled multicentre field study of which *H. contortus* was a component, and studies characterising the plasma profile of eprinomectin following administration of LONGRANGE thereby allowing a relationship between eprinomectin exposure and persistent efficacy against *H. contortus* to be established. In the absence of further supportive data the applicant withdrew the claim for *T. colubriformis* (predominant ovine parasite species).

In both studies animals accepted the treatment well, and local swellings at the injection site resolved within one day after treatment.

Induced infection (shoulder injection)

Eight GCP compliant, controlled randomised studies were conducted to demonstrate the persistent efficacy of LONGRANGE against nematodes after single subcutaneous injection in front of the left or right shoulder at a dose of 1 mg/kg bw. All the studies were conducted in the USA. Two studies were designed to demonstrate the efficacy of LONGRANGE in the prevention of induced infections with immature (L3) nematodes for the duration of 100 days or 120 days, 4 studies for the duration of 120 days, and 2 studies for the duration of 150 days All studies were designed and conducted following the recommendations of VICH GL7 and GL12.

Healthy beef calves of different breeds, aged 4–7 months were used which were initially naïve for worms as determined by standard FEC examination and held under conditions which were designed to preclude any nematode infection. Control treatment (vehicle or saline) and test treatment were administered on D0 in one study and on D0 and D+20 in another study.

On D+120 (or D+150) all calves were challenged with a range of L3 larval nematodes (within one study all calves received the same range of nematode species).The animals were euthanized approximately 3-4 weeks after challenge, corresponding to the pre-patent period of the nematodes. Efficacy was evaluated on the basis of counting of parasites collected from lungs, abomasa, small and large intestines (including caecal portion).

Sufficient efficacy (i.e. statistically significantly fewer nematodes compared to controls, efficacy rate >90%) in the prevention of induced L3 nematode infections at D+120 was demonstrated for *Dictyocaulus viviparus, H. contortus, Trichostrongylus colubriformis*, *Bunostomum phlebotomum*, and *Ostertagia ostertagi*.

Sufficient efficacy in the prevention of L3 nematode infections at D+100 after treatment was demonstrated for *C. oncophora, C. punctata,* and *Trichostrongylus axei* . Efficacy against induced *Haemonchus placei* infection proved to be insufficient in this study.

Sufficient efficacy in the prevention of L3 nematode infections on D+150 after treatment was demonstrated for *Bunostomum phlebotomum*.

Natural infection (shoulder injection)

Four GCP compliant saline-controlled randomized studies were conducted to demonstrate the efficacy of LONGRANGE at a single subcutaneous dose of 1 mg/kg bw (1ml/50kg bw) into the shoulder against established natural nematode infections in beef cattle. One study was conducted in Germany, another one in the UK, and two studies were conducted in the USA (). Healthy worm-free calves of different breeds, aged 4-6 months were used. Following treatment on D0 the animals were exposed to natural mixed nematode infections by grazing on infected pasture from D0 to D+120. Pasture contamination was confirmed by herbal counts, faecal egg counts from study animals (D-14, 0, +28, +56, +84, +120) and worm counts from untreated tracer calves kept on the same pasture. On D+120 the study animals were removed from pasture and placed under conditions designed to preclude further nematode infections. The animals were euthanized on D+147-149 and parasites collected from lungs, abomasa, small and large intestines and identified, specified and counted. Standard procedures and techniques employed complied with VICH and WAAVP guidelines. Data analysis involved calculating the geometric mean of faecal egg counts (FEC) and worm counts per treatment group. Efficacy calculation on species/developmental level was performed according to VICH GL7. Untreated control calves proved to be generally infected with worms of the genera *Dictyocaulus, Ostertagia, Trichostrongylus, Cooperia, Haemonchus, Nematodirus, Bunostomum, Oesophagostomum,* and *Trichuris*.

Significant worm count reduction and efficacy rates above 90% were achieved for adult *B. phlebotomum; Cooperia spp. (C. oncophora/ surnabada, C. punctata)*, adult and L4; *D. viviparus*; *H. contortus*; *N. helvetianus*; *Oes. radiatum, Ostertagia (O. ostertagi/lyrata), Ostertagia* inhibited L4; *T. axei; T. colubriformis.*

Conclusions (persistent efficacy)

A number of studies investigating the persistent efficacy of LONGRANGE administered into the shoulder or at the back of the ear have been provided. However, due to the different plasma time curves of eprinomectin following injection at the back of the ear compared to shoulder injection, the studies (efficacy for up to 100/120 days) using the shoulder injection cannot be extrapolated to the ear injection.

However, in line with the VICH guidelines two well-designed and conducted dose confirmation studies with the ear injection have been provided. The results of these two studies confirm the persistent efficacy of LONGRANGE at a single subcutaneous dose of 1 mg/kg bw for up to 120 days against

D. *viviparus, O. ostertagi, and B. phlebotomum*, and for up to 100 days for *C. oncophora, C. punctata, O. radiatum* and *T. axei.* Although persistent efficacy for *H. contortus* for up to 120 days was only demonstrated in one dose confirmation study, the CVMP agreed with the persistent efficacy period of up to 120 days for this blood sucking nematode species taking into account both the results of the well-controlled multicenter field study and studies characterizing the plasma profile of eprinomectin following administration of LONGRANGE thereby allowing a relationship between eprinomectin exposure and persistent efficacy for *H. contortus* to be established.

Ectoparasites

Efficacy tests investigating the immediate (therapeutic) efficacy of LONGRANGE against ectoparasites (naturally or artificially infested) was demonstrated in studies conducted in the EU and USA, either using the final LONGRANGE formulation (but shoulder injection only) or eprinomectin administered at 0.5 mg/kg bw as a pour-on solution. Based on pharmacokinetic data (see above, pharmacokinetics), extrapolations of these results were accepted by the CVMP in support of the immediate (therapeutic) efficacy in young animals, since initial peak plasma levels after ear injection were shown to be equal or even higher to those obtained after pour-on administration or shoulder injection at the recommended dose. The applicant also confirmed that the susceptibility of the parasite strains tested was comparable between Europe and USA. Long-term efficacy (persistency effect) against ectoparasites was not investigated.

Warble fly *(Hypoderma* spp.) (shoulder injection)

Efficacy of LONGRANGE 50 mg/ml for injection against warble fly larvae was demonstrated in four GCP compliant dose confirmation studies in naturally infected animals after subcutaneous administration of 1 mg eprinomectin/kg bw in the shoulder. Design and conduct of these studies complied with the recommendations of the CVMP guideline on specific requirements for ectoparasiticides in cattle (EMEA/CVMP/625/2003). Cattle used in these studies were sourced from regions known to be endemic for *Hypoderma* (H.) spp. All animals were confirmed positive for the *Hypoderma* infection by ELISA test before study commencement.

H. bovis:
The efficacy of LONGRANGE against *H. bovis* L1, L2, and L3 warble fly larvae (parasitic stages) was demonstrated in two GCP compliant dose confirmation studies, one performed in Germany and another one in the USA reflecting regional differences in livestock breeding and climate. In both studies 100% efficacy was calculated against each of the three larval stages. Three groups each of 10 randomly allocated animals were formed. One group served as vehicle control group (group 1), while the other two groups were treated when the larvae of *Hypoderma* spp. were assumed either to be in the L1 stage of development (group 2, D+0) or when the *Hypoderma* spp. larvae were in the L2/L3 stage of the *H. bovis* life cycle (group 3, D+119 or D+140). Cattle were examined weekly on D119 to D195 or D80 to D129, respectively).

To further support the claimed indication, three additional non-GCP dose confirmation studies were provided using a pour-on formulation at a topical dose of 0.5 mg eprinomectin/kg bw. In these studies 100% efficacy against the L1-L3 migrating stages of *H. bovis* was demonstrated.

H. lineatum:
The efficacy of eprinomectin against *H. lineatum* (parasitic stages L1, L2, and L3) was demonstrated in two GCP compliant dose confirmation studies, one performed in Italy, and another one in the USA. In the USA study, two groups of cattle (group 1 vehicle control, group 2 treatment) were treated subcutaneously in the shoulder when the larvae of *H. lineatum* were expected to be in the L1 stage of

development. A third group was treated subcutaneously in the shoulder with LONGRANGE on D+73 when the migrating larvae were in the L2/L3 stage of development.

In the EU study 5-8 months old cattle naturally infested with *Hypoderma lineatum* were sourced from a known endemic area in Italy. Cattle were treated subcutaneously once in the left shoulder with 1 mg eprinomectin/kg bw (LONGRANGE final formulation) either on D0 (group 2) when the larvae where in the L1 stage, or on D+109 (group 3), when the larvae where expected to be L2/L3. Group 1 served as untreated control. All treated cattle had zero live *Hypoderma* spp. larval counts, while live *H. lineatum* larvae (n=1 -9 larvae/animal) were collected from nine out of the 12 control cattle. In both studies efficacy was calculated to be 100% against each of the three parasitic larval stages claimed for *H. lineatum*.

In addition, three additional non GCP-compliant dose confirmation studies using an eprinomectin pour-on formulation were submitted as supportive information. In these studies performed in Canada and the USA the efficacy was equally 100% against *H. lineatum* L1, L2, and L3 larvae.

In conclusion, the therapeutic efficacy of LONGRANGE against parasitic stages (L1-L3) of both, *H. bovis* and *H. lineatum* was demonstrated according to the CVMP ectoparasitic guidelines (7AE17a) and the guideline on specific requirements for ectoparasiticides in cattle (EMEA/CVMP/625/2003).

Lice (*Linognathus vituli*, *Haematopinus eurysternus*, *Solenopotes capillatus*)

The applicant submitted seven non-GCP compliant dose confirmation studies in naturally infested young beef/dairy cattle (up to 1 year) to justify immediate (therapeutic) efficacy against lice (*Linognathus vituli, Haematopinus eurysternus, Solenopotes capillatus)* after a single pour-on application of 0.5 mg eprinomectin/kg bw along the backline. The studies were conducted in the 1990s in Germany (2 studies) and the USA (5 studies) according to the state of the art at that time. The study period was 56 days and, therefore, covered two full live cycles of lice. The efficacy rate on D+56 was 82.1% in one study, but 100% in the other studies. Although the studies are rather old, they can be accepted as surrogates as there is no published report on eprinomectin resistance in cattle lice until today.

Based on the pharmacokinetic data available after pour on application, the CVMP accepted extrapolation from the immediate efficacy data obtained with the pour-on formulation for the treatment of blood sucking lice. The immediate (therapeutic) efficacy of LONGRANGE against sucking lice is, therefore, considered to be confirmed by these studies.

Horn flies (*Haematobia irritans)*

For the demonstration of the efficacy of LONGRANGE for the treatment of horn fly infestations, the applicant submitted two GCP compliant, negative controlled, blinded, randomized dose confirmation studies, and four supportive non-GCP “pour-on” dose confirmation studies.

The two GCP compliant dose confirmation studies were conducted in the USA, respectively, and meet the recommendations of the CVMP guidelines on the demonstration of efficacy of ectoparasiticides (7AE17a) and the CVMP guidelines on specific requirements for ectoparasites in cattle (EMEA/CVMP/625/2003). The efficacy against horn flies was confirmed after a single subcutaneous injection of 1 mg eprinomectin/kg bw at the shoulder. In these studies the final formulation of LONGRANGE was used and achieved immediate efficacy rates of 91.8% and 98.2% between D+2 and D+6 after treatment.

The results of these two studies can be extrapolated to the administration of LONGRANGE at the back of the ear, because comparable eprinomectin plasma levels in the first 10 days post-treatment are achieved after injection at the back of the ear compared to the injection in front of the shoulder. In

order to demonstrate adequate efficacy for the first 48 hours after administration of the product, the applicant submitted an abbreviated study report of one non-GCP horn fly study. Due to major shortcomings of the study (only 4 animals/group, no information about the laboratory strain, incomplete study documentation) valid conclusions relating to the efficacy of LONGRANGE against horn flies for the first 48 hours after administration cannot be drawn. Furthermore, the applicant submitted only one dose confirmation study, which is not in line with the guideline (EMEA/CVMP/625/03/Final). Consequently, corresponding information should be included in section 4.4 of the SPC: *"The efficacy against horn flies was demonstrated from 48 hours after administration of the product onwards"* if authorised.

Four additional studies using the eprinomectin pour-on formulation are considered as supplementary information. These studies were conducted in Canada and in the USA in the 1990s to confirm the efficacy of eprinomectin in the treatment of artificially (1 study) or naturally (3 studies) infested young cattle. The studies were conducted at the state of art at that time. The mean efficacy of the entire study duration (up to 36 days) ranged from 52-77% in these studies. However, adequate immediate efficacy was achieved up to D+14 (98.7–100%) in artificially infested cattle, and up to D+7 (89.5–99.7%) in naturally infested cattle.

Mites (*Sarcoptes scabiei* var. *bovis)*

One GCP compliant pilot conducted in Germany and two GCP compliant dose confirmation studies conducted in Germany and Austria were submitted to confirm the efficacy of LONGRANGE at a single dose of 1 mg/kg bw administered subcutaneously in front of the shoulder against artificial infestation with *Sarcoptes scabiei* var. *bovis*. The standards for study design, choice of animals, number of animals and infestation dose of all three studies complied with the current recommendations of the CVMP guideline on specific efficacy requirements for ectoparasiticides in cattle (EMEA/CVMP/625/2003), and followed the WAAVP guidelines for evaluation the efficacy of acaricides against mange and itch mites on ruminants (2006). Efficacy was evaluated up to 8 weeks using the following parameters: weekly live mite counts, body weight and weight gain, and lesion scores on D+56. At all post-treatment study days mite counts were significantly ($p<0.05$) lower in treated cattle compared to the negative controls, and 100% efficacy was demonstrated.

Treatment with LONGRANGE was well-tolerated by all study animals.

Target animal tolerance

Tolerance of cattle to LONGRANGE has been examined in the pivotal target animal safety study after subcutaneous administration of a single dose of LONGRANGE (1 ml/kg bw) in front of the shoulder (not the back of the ear, as proposed for this application) in young beef cattle. In addition, the applicant provided safety data with LONGRANGE injection in the back of the ear from other preclinical and clinical studies.

Pivotal target animal safety (TAS) study

In the pivotal target animal safety (TAS) study, safety of 24 healthy male and female 6–7 months old Angus calves to LONGRANGE was investigated, when injected in front of the shoulder at 0 (vehicle only), 1x, 3x, and 5x the recommended treatment dose (RTD) of 1 mg/kg bw. The 3x RTD and 5x RTD doses were injected, at 3 or 5 sites respectively, 10 cm apart. Animals were regularly clinically examined and blood was sampled for blood chemistry/haematology and also determine eprinomectin plasma levels up to D 120-122 (necropsy).

The product was generally well tolerated. No general health problems were reported in this study; however, a slight decrease of red blood cells within the normal range was noted at 1x RTD. At 3x and 5x RTD, this decrease was statistically significant but not clinically relevant. Corresponding information has been added in section 4.10 of the SPC.

Feed consumption and body weight gain were significantly reduced at 3x and 5x RTD overdoses; however, the observed changes in the body weight were minor and attributable to normal biologic variations of growing cattle.

At all doses, reactions at the injection sites could be seen (mild oedema without pain, hyperaemia or skin necrosis) up to several weeks. Necropsy findings showed subcutaneous granular foci in one or more injection sites. Appropriate information is included in the SPC and product literature.

Repeated injections of the proposed treatment dose of LONGRANGE have not been examined. Thus, the treatment frequency of LONGRANGE should be restricted to a single administration within one grazing season. This is in line with the correct and prudent use of the product, which is designed to treat and prevent nematode infestations during the first part of the grazing season, then leaving time for the development of a sensitive population to dilute the selected resistant worms. This information has been provided in the product literature.

As the study was not performed using the recommended route of administration (ear injection), and in line with a CVMP scientific advice, the applicant justified the use of the "shoulder data" with the pharmacokinetic behaviour of eprinomectin following injection at different sites. The applicant calculated that eprinomectin plasma kinetics following a 5x RTD overdose "shoulder" injection in calves would correlate with a 3x RTD overdose following "ear" injection. Since 5x RTD overdoses were well tolerated in the pivotal TAS study, LONGRANGE could therefore be considered to be safe at 3x RTD overdose when injected at the back of the ear.

The CVMP agreed that although the safety of LONGRANGE after injection at the back of the ear at overdoses was not determined experimentally, safety of overdoses after ear injection could be extrapolated based on pharmacokinetics of eprinomectin due to the assumption of dose-linearity. The applicant's argumentation could therefore be accepted with regard to beef calves.

Adult cattle

- No margin of safety could be derived for LONGRANGE in regard to adult lactating animals. The TAS study did not include adult, lactating cattle, and extrapolations from other studies based on pharmacological data were not considered appropriate: the initial maximum plasma level of eprinomectin in lactating dairy cattle after injection of the therapeutic dose (1x RTD) in the back of the ear is higher than the maximum plasma level at the 5x RTD dose in calves after shoulder injection in the TAS-study .
- The mean plasma concentrations of eprinomectin in lactating cattle within the first 42 days after injection of the therapeutic dose in the back of the ear (1x RTD) were similar to levels at the 3x RTD and the 5x RTD dose in calves after shoulder injection in the TAS-study.

Therefore, the systemic tolerance of lactating cows to LONGRANGE over the proposed duration of activity of 120 days cannot be derived. Since no data demonstrating persistent efficacy and a margin of safety has been provided, lactating cattle were removed from the product information.

Young calves

The safety of this product has not been investigated in calves younger than 3 months. Corresponding information has been included in SPC in section 4.5.

Local tolerance of LONGRANGE

The applicant conducted an injection site safety study, which is in accordance with VICH guideline 43.

In this study, LONGRANGE was injected once subcutaneously at the back of the ear to eight female Holstein calves at the proposed dose followed by a 42-day observation period. Each animal served as its own control, as one ear was treated with LONGRANGE whereas a vehicle control has been injected to the other ear. A maximum volume of 10 ml was tested in this study. Accordingly, the applicant added 10 ml as the maximum tolerable volume injectable at the back of the ear to section 4.9 of the product literature.

The test product was administered once only, i.e. multiples of the proposed treatment frequency have not been examined, therefore the frequency of LONGRANGE treatment should be restricted to a single administration within one season. This information has been provided in the SPC section 4.9.

Local tolerance has been adequately assessed clinically by macroscopic and palpatory examination of the injection sites at 1, 2, 3, 7, 10, 14, 21 and 28 days after treatment. Thereafter, affected animals were examined weekly until complete resolution of any injection site reaction. Injection sites were scored for pain response, hyperthermia, oedema/swelling, skin necrosis as well as for behaviour and movement of the ear.

Injection sites showed moderate swellings up to 42 days. Pain at injection the site was detected in two animals at day 7. No bleeding was visible in any animal throughout the study. However, heat at the injection site was recorded in 6 animals up to day 7.

In summary, study data show that the product induces swelling, heat and pain very commonly when administered at the back of the ear which resolved without intervention within 4-6 weeks. Corresponding information is included in the SPC and other product information.

Reproductive safety of LONGRANGE

(1) Reproductive safety in female breeding cattle

No reproductive safety study with LONGRANGE after injection at the back of the ear has been conducted.

However, two reproductive safety studies , in which LONGRANGE was injected subcutaneously at the front of the shoulder of female beef cattle have been provided. Moreover, the applicant submitted two studies, a reproductive safety study and a pharmacokinetics study, conducted with a topical formulation of eprinomectin to support reproductive safety of LONGRANGE. Although the results obtained from these trials would not raise any safety concerns with regard to fertility and/or reproduction, an extrapolation of safety data from studies using other doses and administration routes was not considered adequate to demonstrate reproductive safety of the product after administration at the back of the ear, due to different pharmacokinetics.

However, by comparing plasma profile curves generated following s.c. injection of the recommended dose at the back of the ear with those generated in 13 studies following shoulder injection, LONGRANGE ear injection demonstrated statistically significantly higher plasma levels than the shoulder injection for 10 weeks after dosing. There was no statistically significant difference in plasma concentrations from Day 70 onward.

Considering that reproductive safety has been demonstrated for the 3x dose level after shoulder injection, it is agreed that plasma levels at day 70 following the injection of the proposed label dose at the back of the ear, being equal or lower to the 1x dose after shoulder injection, should bear no risks

for the reproduction of female cattle (conception, embryonic and foetal phase).

Notably, this approach does not include the follicular phase before conception. However, the large data base of toxicological data did not demonstrate an impact on the folliculogenesis in laboratory animals, and thus, this approach is accepted.

Based on the data presented information should be included in the SPC and other product information if authorised that no reproductive safety studies have been conducted with the product injected at the back of the ear and it is therefore not recommended to treat pregnant animals and to breed animals before 10 weeks after administration of the product.

In addition, it is noted that the product contains N-methylpyrrolidone (NMP), which has recently been classified as toxic for reproduction by the European Chemicals Agency (ECHA). However, during a single application of LONGRANGE, cattle receive an NMP dose which is far below the NOEL values in the rat studies reviewed by ECHA. Moreover, NMP was rapidly depleted following injection of LONGRANGE, showing that the formulation with PLGA does not impact the fast metabolism and excretion of NMP. Further, this dose of NMP was demonstrated to be safe when administered in LONGRANGE to breeding cattle via shoulder injection, which has the same rapid excretion profile for NMP as the ear injection. Thus, it is considered that NMP will not impact the reproductive safety profile of LONGRANGE.

(2) Reproductive safety in male breeding cattle

No data have been provided with respect to male cattle intended for breeding. Section 4.7 has been amended with the wording: “The safety of the product has not been tested in breeding age bulls, therefore the use of the product is not recommended in breeding bulls”.

Clinical field trials

Clinical studies

Nematodes

The applicant submitted one pivotal EU field study from 2015 to evaluate the safety and efficacy against gastrointestinal nematodes (strongylids, *Nematodirus* spp., and / or *Dictyocaulus viviparus*), when administering LONGRANGE at the back of the ear.

In addition, seven field studies were submitted to confirm the efficacy of LONGRANGE against natural nematode infections in cattle when administered subcutaneously in the shoulder. All study sites were located in the USA, and regional climates, cattle breeds, housing practices as well as parasite population may, therefore, differ from EU conditions. In addition, the studies were conducted in 2001, which is more than 10 years ago, and resistance of certain nematodes against avermectins could have arisen in the meantime, although the CVMP is not aware of any eprinomectin resistances being described for cattle. For the stated reasons and because the PK profile of eprinomectin considerably differs from the “ear injection”, the studies are only considered as supportive regarding the persistent efficacy assessment of LONGRANGE.

Prd0323301-04: Effectiveness of Eprinomectin (5% w/v) extended – release injection (1 mg/kg body weight) administered as a single subcutaneous dose on the back of the ear against natural infections of nematode endoparasites of cattle under field conditions.	
Objectives	To confirm the efficacy and safety of eprinomectin (5% w/v) extended-release injection when administered once subcutaneously at the back of the ear at 1 mg/kg body weight as a solution to cattle

	against natural nematode endoparasite infections under field conditions.
Study sites	Germany (2 sites); France (2 sites)
Study design	negative controlled, blinded, multicentre
Compliance with regulatory guidelines	VICH GL 9, VICH GL7, and VICH GL12
Treatment	Group 1: control group (saline - 0.9% w/v NaCl) 1 ml/50 kg bw, subcutaneous injection at the back of the right ear; Group 2: LONGRANGE 1 ml/50 kg bw, subcutaneous injection at the back of the right ear (the calculated dose was rounded up to the next 0.2 ml increment, as appropriate)
Animals	156 healthy, ruminating cattle, 111 male and 45 female, 6-14 months old, 139 – 334 kg bw Breed: Pinzgauer (n=48, Site 01), Brown Swiss (n=48, Site 02), Montbéliarde (n=32, Site 03), Prim Holstein (n=28, Site 04)
Eligibility criteria	Naturally infection with gastrointestinal nematodes (strongylid, 154/156, Nematodirus, 39/156, and/or Dictyocaulus viviparus, 87/156) based on D-5 faecal egg and lungworm larval count
Outcomes/endpoints	Primary endpoint: Faecal egg count (FEC) and lungworm larval count determination at D+28, D+56/57, D+84, D+99/100, D+119/120. Secondary endpoint: body weight gain
Statistical method	FEC and larval counts: Geometric means were used (count+1) Efficacy (%) = (Control group-Treatment group)/(Control group) x 100 All testing were two-sided at the significance level α=0.05 Nematodirus, Trichuris, Strongyloids nematode egg counts: No analyse at all post-treatment time points, because the infection rate was <40% in the control group Dictyocaulus larval counts: No Dictyocaulus lungworm larvae have been identified on study site 03 and 04, therefore, the parasite count was excluded from analysis for these study sites.

Results	
Outcomes for endpoints	**Table 7. Analysis of Strongylid Egg Counts by Site**

Study Day	Site	Group 1[1] GM[4]	Group 2[2] GM	Percent Efficacy[3]	P-value[5]
28	01	137.8	0.0	100.0	<0.0001
	02	131.7	0.0	100.0	<0.0001
	03	9.8	0.3	96.5	<0.0001
	04	41.8	0.4	99.1	<0.0001
56	01	66.0	0.1	99.9	<0.0001
	02	227.0	0.1	>99.9	<0.0001
	03	14.6	0.4	97.1	<0.0001
	04	53.8	0.4	99.3	<0.0001
84	01	145.6	0.0	100.0	<0.0001
	02	52.2	0.1	99.9	<0.0001
	03	19.6	2.1	89.4	0.0048
	04	12.3	0.0	100.0	<0.0001
100	01	98.3	0.1	99.9	<0.0001
	02	70.6	0.0	100.0	<0.0001
	03	2.9	1.0	64.6	0.2069
	04	5.6	0.1	97.5	0.0005
120	01	162.9	0.2	99.9	<0.0001
	02	35.9	0.0	100.0	<0.0001
	03	12.1	1.5	87.6	0.0003
	04	18.9	1.2	93.6	0.0004

[1] Group 1 = Saline-treated control (Day -5, 28, 56, 84, 100: n=39; Day 120: n=38).
[2] Group 2 = Eprinomectin (5% w/v) ERI (n=117).
[3] Percent efficacy = 100 x [(C-T)/C], where C is GM of group 1 and T is GM of Group 2.
[4] GM = geometric mean, computed by subtracting 1 from the anti-logarithm of the mean of ln(count+1).
[5] P-value = Treatment effect probability value from analysis of variance on log-counts for Treatment Group 2 and Treatment Group 1.

Table 3. Analysis of *Dictyocaulus* Lungworm Larval Counts with Site 1 and Site 2 only

Study Day	Group 1[1] GM[4]	Group 2[2] GM	Percent Efficacy[3]	P-value (interaction)[5]	P-value (treatment)[6]
-5	0.77	0.85	NC[7]	NC[7]	NC[7]
28	3.62	0.00	100.0	<0.1309	<0.0001
56	4.36	0.00	100.0	<0.0001	--[8]
84	3.95	0.00	100.0	<0.8146	<0.0001
100	1.61	0.00	100.0	<0.1226	<0.0001
120	0.61	0.00	100.0	<0.0590	<0.0001

[1] Group 1 = Saline-treated control (Day -5, 28, 56, 84, 100: n=24; Day 120: n=23).
[2] Group 2 = Eprinomectin (5% w/v) ERI (n=72).
[3] Percent efficacy = 100 x [(C-T)/C], where C is GM of group 1 and T is GM of Group 2.
[4] GM = geometric mean, computed by subtracting 1 from the anti-logarithm of the mean of ln(count+1).
[5] P-value(interaction) = Treatment-by-site interaction probability value from analysis of variance on log-counts for Treatment Group 2 and Treatment Group 1.
[6] P-value(treatment) = Treatment effect probability value from analysis of variance on log-counts for Treatment Group 2 and Treatment Group 1.
[7] Not calculated.
[8] Due to the significant treatment-by-site interaction, treatment effect was evaluated by site separately in Table 4.

	Table 6. Analysis of Weight Gain (kg)[1] | Study Day | Group 1[2] LSM[4] | Group 2[3] LSM | P-value[5] | |---|---|---|---| | 28 | 17.4 | 18.1 | 0.8002 | | 56 | 22.9 | 26.7 | 0.2367 | | 84 | 32.4 | 41.4 | 0.0197 | | 100 | 36.5 | 51.2 | 0.0018 | | 120 | 42.7 | 57.7 | 0.0167 | [1]Weight gain is derived by subtracting the pretreatment (from Day -5 or Day -1) weight from the weight on each study day. [2] Group 1 = Saline-treated control (Day -5, 28, 56, 84, 100: n=39; Day 120: n=38). [3]Group 2 = Eprinomectin (5% w/v) ERI (n=117). [4]The least square means of weight gain for each study day and each treatment group. [5]P-value: Probability value of analysis of variance for a generalized randomized block design.
Adverse events	No study animals showed adverse events related to treatment. At site 01, group 1 animal (ID#2496) was found dead on D+100. Necropsy including parasite counts revealed parasitic gastroenteritis and lungworm disease.
Conclusion of the applicant	The efficacy and systemic safety of the treatment with eprinomectin (5% w/v) ERI at 1 ml/ 50 kg bw when administered once s.c. on the back of the ear to cattle naturally infected with gastrointestinal nematodes and *D. viviparus* lungworms were excellent (strongylid eggs efficacy: 98.8 – 99.8, *Dictyocaulus* efficacy: 100%) under field conditions.

The efficacy and safety of LONGRANGE has been examined in a GCP compliant, randomized, negative controlled, blinded, multicentre field study conducted in Europe and carried out in compliance with the principles of VICH GL9 (GCP), and VICH GL7 (Efficacy of anthelmintics: general requirements), and VICH GL12 (Efficacy of anthelmintics: specific recommendations for bovines). A total of 156 young cattle, beef as well as dairy cattle breeds, aged between 6–14 months, 139-334 kg bodyweight with natural infections of nematode endoparasites have been treated with a single injection of LONGRANGE at the back of the ear. The efficacy of the treatment was monitored over a period of 120 days.

In general, the design and the conduct of the study are acceptable. The choice of the study areas (Germany and France) is justified with the intense cattle farming in both countries. Furthermore, the sites are representative for three different geographical habitats (lowland farming, Alpine foreland farming, mountain farming) and include common and regional cattle breeds but also breeds of only locally restricted interests. Examination of faeces before study start revealed that all study animals were infected with gastrointestinal nematodes as well as with lungworms. Throughout the study, the animals grazed on pastures with a history of natural nematode infections. Pairs of sentinel animals were grazed with the study animals at each site. Necropsy of the sentinel animals at different time points revealed a variety of gastrointestinal nematodes such as *Haemonchus*, *Ostertagia* spp., *Cooperia* spp.,

Nematodirus spp., *Trichuris* spp., *Bunostomum* spp. as well as *Dictyocaulus*. These data indicate that all study animals (independent from site) have been exposed to gastrointestinal parasites for the whole study period.

The study results indicate that the claim of an immediate therapeutic efficacy of LONGRANGE is justified in calves, as efficacy rates (based on strongylid FEC) are above 95% at all study sites on D+28. However, efficacy rates dropped below 90% after D+56 at study site 3 representing 20% of the total study population. It is however acknowledged that at this study site the FEC in the control animals was low during the course of the field trial, contributing at least in part to the insufficient efficacy results at this study site.

A statistically significant increase in the bodyweight gain of the animals of the test group was also noted in the field study. However, the observed changes in body weight are minor and most likely attributable to normal biologic variations of growing cattle as well as to the elimination of the gastrointestinal parasites followed by an improvement of nutrient utilization from the gut of the eprinomectin treated groups.

Conclusions

Nematodes

The results of the well-conducted field study supported by dose-confirmation studies show that the claim for immediate therapeutic efficacy of LONGRANGE is justified in young ruminant cattle, as efficacy rates are above 95% at all study sites on D+28 against the claimed gastrointestinal roundworms (adults and L4: *Ostertagia spp., Cooperia spp., Haemonchus spp., Trichostrongylus colubriformis, Bunostomum phlebotomum, Nematodirus helvetianus, Oesophagostomum radiatum)* and lungworms (adults and L4): *Dictyocaulus viviparus.*

Dose-confirmation studies also demonstrated adequate efficacy in the prevention of reinfections with the following helminths: *Dictyocaulus viviparus, Ostertagia ostertagi/lyrata*, *Haemonchus contortus* and *Bunostomum phlebotomum* for up to 120 days; O*esophagostomum radiatum, Cooperia oncophora/surnabada, Cooperia punctata* and *Trichostrongylus axei* for up to 100 days.

Ectoparasites:

No field studies investigating the efficacy of LONGRANGE against ectoparasites have been submitted, which is acceptable since dose confirmation studies used either animals with natural infestation (*Hypoderma spp.*), or bridging data (*Linognathus* and *Solenopotes spp*.) to confirm the efficacy. Regarding sarcoptic mange, it is generally accepted, that this parasite species is not common under field conditions.

Therefore, the CVMP agreed that demonstration of efficacy in dose confirmation studies was considered sufficient to demonstrate the immediate (therapeutic) efficacy of LONGRANGE against the claimed ectoparasites (Warbles (parasitic stages): *Hypoderma bovis*, *Hypoderma lineatum;* Mange mites: *Sarcoptes scabiei* var*. bovis;* Sucking lice: *Linognathus vituli, Haematopinus eurysternus, Solenoptes capillatus;* and Horn flies: *Haematobia irritans).*

Overall conclusion on efficacy

Pharmacodynamics

Eprinomectin is an endectocide with killing activity against gastrointestinal nematodes, lungworms, fleas, warbles (parasitic stages), mange mites, lice and horn flies. The mode of action has been

sufficiently described. Like for other avermectins, the anti-parasitic effect of eprinomectin is thought to be mediated by its selective, high affinity binding to glutamate-gated chloride channels that are present in invertebrate nerve and muscle cells. Binding leads to an increase in the permeability of the cell membrane to chloride ions causing hyperpolarization of affected cells and subsequent paralysis and death of the parasite.

Resistance

Although gastro-intestinal resistant nematodes to eprinomectin in cattle are reported in the USA, New Zealand and Brazil, no information is available in the European Union. However the use of this long-acting product may be particularly associated with the risk of resistance development in nematode species because of the gradual eprinomectin depletion at the end of the prolonged-release period. The applicant's proposal of targeted selective treatment in order to reduce this risk was in principle acknowledged by the CVMP. However, the committee did not accept the proposal to leave 20% of the animals in a herd untreated, as a rule, because this approach was primarily derived from a matrix model on dung fauna and no data in cattle demonstrating the impact on the development of resistance has been provided. The committee felt that the decision on how many animals in a herd should be left untreated to maintain a susceptible worm population on pasture should be made by the responsible veterinarian on the farm, taking into account factors that may influence any strategy to maintain susceptible parasite population on pasture, such as the pathogenicity of the parasite species, the herd size and pasture stocking, pasture contamination etc.

Pharmacokinetics

The pharmacokinetic properties of eprinomectin are well known. It is not extensively metabolized, it is highly bound to plasma proteins (>99%) and distributed in the body in various organs. It is excreted mainly via the faeces in a pattern mirroring the plasma levels. A very small amount is excreted via the urine. It can also pass the blood-milk-barrier.

LONGRANGE contains eprinomectin in a polymer-based formulation, resulting in a prolonged release. Following subcutaneous injection a biphasic plasma curve is noted; after a high initial peak (D 1-3), plasma levels drop over the following weeks, followed by a second peak (D 70-90), and the final elimination phase.

However, the shape of the plasma time curve varies between individuals. Also, differences in the extent of the plasma levels were noted in regard to different injection sites and different age or breed groups of animals after subcutaneous injection at the base of the ear.

In lactating dairy cattle, maximum measured plasma concentrations at the initial peak are considerably higher than in young beef cattle (about 2-fold), and plasma level data are not available beyond D56. In consequence, the existence, time and shape of the second peak is unknown, as well as at what time plasma levels would decline below the limit of detection.

Absorption pharmacokinetics and the plasma time curves also differ considerably between injection sites (back of the ear versus front of the shoulder).

Dose determination

The dose of eprinomectin was chosen based on a dose determination study investigating the pharmacokinetic profile and efficacy of the test formulation at a single subcutaneous dose of 0, 0.5, 0.75 or 1 mg/kg bw in the front of the shoulder. The results do not support the proposed treatment dose of 1 mg/kg bw since sufficiently high efficacy against induced nematode infections at day 120 post-dose was already achieved with the lowest dose tested. A sound justification of the recommended

treatment dose is missing, and the selected treatment dose may not be the optimum one from an efficacy perspective. Given, however, that immediate and persistent efficacy has been demonstrated after administration at the recommended dose of 1 mg/kg bw at the back of the ear for gastrointestinal nematodes and lungworms in a sufficient number of dose confirmation studies, supported by a field study, the recommended dose 1 mg/kg bw s.c. at the back of the ear is accepted.

Tolerance

Systemic Tolerance

The target animal safety study demonstrated the safety of LONGRANGE at the recommended treatment dose (RTD) of 1 mg/kg bw and multiples (3x RTD and 5x RTD), when injected subcutaneously in front of the shoulder of beef calves. Apart from transient injection site reactions, doses of up to 5x RTD were generally well tolerated. Assuming dose-linear kinetics of eprinomectin after subcutaneous injection of LONGRANGE, similar eprinomectin plasma concentrations in calves are anticipated for the 3x RTD overdose (injected in the ear) and the 5x RTD overdose (injected in the front of the shoulder), and a calculated 3x RTD overdose (injected at the back of the ear) is therefore considered well tolerated in calves. This was confirmed by the field efficacy study.

Since no tolerance data have been provided for lactating cattle, these animals were removed from the product information.

The safety of this product has not been investigated in calves younger than 3 months. Corresponding information has been included in the product information in section 4.5.

Local Tolerance

The local tolerance to LONGRANGE at the therapeutic dose in the back of the ear has been examined in an injection site safety study in compliance with VICH GL43. Information with regard to the maximum volume to be injected as well as to the patho-morphological changes at the injection sites have been provided in the product literature.

Reproductive Tolerance

By comparing plasma profile curves generated following administration of the recommended dose at the back of the ear with those generated in studies following shoulder injections, statistically significantly higher eprinomectin plasma levels were observed for 10 weeks after dosing following ear injection, but no statistical difference in eprinomectin plasma concentrations was demonstrated for both administrations routes from day 70 onward. Considering that reproductive safety has been demonstrated for the 3x dose level after shoulder injection, plasma levels at day 70 following the injection at the back of the ear, being equal or lower to the 1x dose after shoulder injection, should bear no risks for the reproduction of female cattle (conception, embryonic and foetal phase). Appropriate information should be included in the product literature, if authorised, indicating that no reproductive safety studies have been conducted with the product injected at the back of the ear and it is not recommended to treat pregnant animals and to breed animals before 10 weeks after administration of the product.

The product includes the excipient N-methylpyrrolidone (NMP), which has been recently classified as toxic for reproduction by ECHA. Considering that NMP is administered in a single dose far below the NOEL values in the rodent studies reviewed by the ECHA, is rapidly depleted from the organism and has moreover been demonstrated to be safe when administered to breeding cattle via a shoulder injection, NMP should not impact the reproductive safety profile of LONGRANGE.

As no data is available to assess fertility and reproduction parameters after eprinomectin treatment in

male cattle, bulls intended for breeding should not be treated with this product. Corresponding information has been added to the product literature.

Efficacy

Immediate (therapeutic) efficacy

Endoparasites

The efficacy of LONGRANGE in the treatment of gastrointestinal nematodes and lungworms as indicated in the SPC, section 4.2, indication, can be derived from a total of 15 GCP compliant dose confirmation studies in calves and young cattle of different beef and cross-breeds following induced larval infection, and established larval and adult infections with gastrointestinal nematodes and lung worms. All studies were performed according to current scientific standards (VICH GL7, GL12).

Ectoparasites

The results of four GCP compliant and six additional non-GCP compliant dose confirmation studies demonstrate the efficacy of the product against parasitic stages (L1, L2, and L3) of both *H. bovis* and *H. lineatum* warble flies.

The results from seven non-GCP studies using a pour on formulation, allow conclusion on the immediate (therapeutic) efficacy (up to 56 days) of LONGRANGE against lice (*Linognathus vituli, Haematopinus eurysternus, Solenoptes capillatus*) in cattle.

The results from two GCP and four supplemental non-GCP dose confirmation studies do allow to conclude on the immediate (therapeutic) efficacy against horn flies (*Haematobia irritans*) in cattle (up to 14 days). However, efficacy for the first 48 hours after application of the product has not been demonstrated based on the data presented and corresponding information needs to be added in the SPC and other product information if authorised.

The results from one GCP compliant pilot and two GCP compliant dose confirmation studies demonstrate therapeutic efficacy of the product against *Sarcoptes scabiei var. bovis* in cattle (up to 56 days).

No field studies are considered necessary to confirm the therapeutic efficacy of the product against ectoparasites, since dose confirmation studies were performed with naturally infested animals (*Hypoderma spp.*) or bridging data (*Linognathus* and *Solenopotes spp*.) were provided to confirm the efficacy. Regarding sarcoptic mange, it is generally accepted, that this parasite species is not very common under field conditions. Therefore, efficacy demonstration in controlled dose confirmation studies is considered sufficient.

Persistent efficacy

Based on the data provided, the efficacy of LONGRANGE in the prevention of reinfections with nematodes and lungworms has been demonstrated in line with the VICH guidelines in two well-designed and conducted dose confirmation studies after administration of LONGRANGE at the recommended dose at the back of the ear. The results of these two studies confirm the persistent efficacy of LONGRANGE for up to 120 days for of D. *viviparus, O. ostertagi, and B. phlebotomum*, and for up to 100 days for *C. oncophora, C. punctata, O. radiatum* and *T. axei.* With regard to *H. contortus*, the committee agreed with a persistent efficacy period of up to 120 days for this blood sucking nematode, based on the results of one dose confirmation study, the results of the well-controlled multicentre field study of which *H. contortus* was a component, and studies characterising the plasma profile of eprinomectin following administration of LONGRANGE thereby allowing a relationship between eprinomectin exposure and persistent efficacy against *H. contortus* to be established for that

time period.

Field efficacy

The pivotal clinical field trial performed in Europe demonstrates both immediate therapeutic and persistent efficacy of LONGRANGE against gastro-intestinal nematodes and lungworms, when administered at the back of the ear to calves at the recommended dose.

However, the impact of the product's use on the development of immunity in the treated animals was not assessed by the applicant. Nevertheless, the intended use of the product under strict conditions of targeted selective treatment (TST) enable both continuous field contamination with nematode eggs from untreated animals and sufficient contact of treated calves with shed nematode eggs particularly at the end of the grazing season. Moreover, the risk of treating animals more than once in their life is prevented by means of age restriction for the product to animals below 18 months.

Part 5 – Benefit-risk assessment

Introduction

LONGRANGE 50 mg/ml is a prolonged-release formulation containing eprinomectin as the active ingredient and is intended for the treatment of gastrointestinal nematode and lungworm infections, warbles (parasitic stages), mange mites, lice and horn flies, and for the prevention of re-infestations with certain gastrointestinal nematode species and lungworms for up to 120 days. The proposed treatment dose is a single subcutaneous dose of 1 mg/kg bw (1 ml/50 kg) to be administered at the back of the ear. The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application).

Benefit assessment

Direct therapeutic benefit

The proposed benefit of LONGRANGE would be its immediate efficacy in the treatment of infestations with gastrointestinal nematodes and lungworms, and ectoparasites (warbles (parasitic stages), mange mites, lice and horn flies), and its persistent effect in the prevention of reinfections with certain gastrointestinal nematode species and lungworms for up to 120 days after treatment.

The proposed indications were investigated in a large number of well-designed laboratory and field studies in young cattle, (mainly beef but also dairy calves) which were, in general, conducted to current scientific standards. However, most of these studies have been conducted with the product authorised in the USA and Canada with a different site of the subcutaneous injection (subcutaneous injection in the shoulder), while the back of the ear is the intended site of injection for the EU LONGRANGE product. Efficacy rates in these studies were well above the threshold recommended in the VICH guidelines.

From the data provided, the immediate (therapeutic) efficacy of LONGRANGE in the treatment of the claimed endo- and ectoparasites (gastrointestinal nematodes and lung worms, warbles, mange mites, lice, and horn flies) could be accepted, as the applicant demonstrated sufficiently similar initial eprinomectin plasma concentrations after injection, either in the shoulder or at the back of the ear. The claimed persistent effect, i.e. prevention of reinfection with certain gastrointestinal nematodes and lungworms has been demonstrated for up to day 100 or 120, depending on the target parasite species.

Additional benefits

LONGRANGE is a prolonged-release formulation that is expected to be administered only once a year at the start of the grazing season, and would therefore reduce the need for repeated antiparasitic treatments of cattle on pasture.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate 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. In general, the dossier takes into account current rules and guidelines. All issues have been resolved and there are no major objections on the quality part of the dossier.

Safety

Risks for the target animal:

In the absence of data, calves younger than 3 months should not be treated with this product.

Adverse reactions comprise of swelling, heat and pain at the injection site, which occur very commonly and resolve without intervention within 4-6 weeks.

As no data is available to assess fertility and reproduction parameters after eprinomectin treatment in male cattle, bulls intended for breeding should not be treated with this product.

As the reproductive safety of the product has not been established before 10 weeks after administration, it is not recommended to treat pregnant animals or to breed animals before that time.

Since no data demonstrating persistent efficacy and a margin of safety has been provided in that subgroup, lactating cattle were removed from the product information.

Special risks

The use of this long acting product may be associated with an increased risk of selection of resistant helminth strains. The applicant's recommendation to leave 20% of the animals in a herd untreated, as a rule, was mainly derived from a matrix modelling approach to predict the potential long-term impact on dung fauna, but no data have been made available to demonstrate the efficacy of this systematic approach in reducing the selection of resistant nematodes.

Risk for the user

A mostly appropriate user safety assessment has been provided. User safety risks have been identified, which are mainly associated with accidental self-injection, but also with accidental eye and dermal contact. However, risk mitigating measures regarding hypersensitivity and developmental toxicity have not been addressed sufficiently in the product literature.

Risk for the environment

A risk was identified for the sediment compartment and for dung fauna. The risk to sediment would be reduced by keeping treated cattle away from lakes and streams for three weeks after treatment and inclusion of corresponding advice in the product literature. However, a risk to dung fauna is indicated due to the long excretion duration of eprinomectin that could prevent recovery of the dung fauna

populations on pastures used by treated animals. The proposed risk mitigation measure to leave 20% of herd untreated, based on population modelling for the yellow dung fly (*Scatophaga stercoraria*) does not allow to conclude with a sufficient degree of certainty on whether the risk mitigation measure is sufficiently protective for dung insects in the long-term. Additionally, it has to be considered that due to the persistence of eprinomectin in dung and environment, the exposure and consequently the risk to dung fauna would also last over and most likely beyond the entire period of persistent antiparasitic activity of this product. Therefore, CVMP concluded that the risk to dung fauna cannot be considered to be mitigated based on the data provided.

Risk for the consumer

Eprinomectin has been evaluated previously in respect to the safety of residues and MRLs have been established for target species and food commodities concerned under this application.

A withdrawal period of 106 days for edible tissues from treated cattle was considered necessary to ensure consumer safety. The product is not proposed for use in lactating animals.

Risk management or mitigation measures

Information relating to potential risks of this product relevant to the target animal would need to be supplemented in the product literature if authorised in order to prevent or reduce potential risks in pregnant and breeding animals.

Based on the data presented it was agreed to mention in the product literature that no reproductive safety studies have been conducted with the product when administered as intended and that it is therefore not recommended to treat pregnant animals and to breed animals before 10 weeks after administration.

In order to minimise the potential risk for the development of resistant helminths, appropriate risk mitigation measures would need to be implemented. This should include a targeted selective treatment concept, where a number of animals in a herd would be left untreated to maintain a susceptible worm population on pasture. The decision on how many animals would need to be left untreated would be made by the responsible veterinarian on the farm, taking into account local epidemiological, clinical and parasitological aspects.

Regarding user safety, warning phrases would need to be supplemented in the SPC and other product information if authorised in order to protect persons with known hypersensitivity to product ingredients as well as women intending to become pregnant, those who are pregnant and those that are breastfeeding.

Regarding consumer safety, a suitable withdrawal period for edible tissues was agreed.

Regarding the environment, suitable information for inclusion in the SPC and other product information were agreed regarding potential risks for aquatic ecosystems and advice on how to prevent or reduce these risks. No appropriate risk mitigation measures could be established to address the risk for dung fauna based on the data presented.

Evaluation of the benefit-risk balance

Information on development, manufacture and control of the active substance and finished product has been presented and leads to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The product has been shown to be efficacious in the control of infections with gastro-intestinal nematodes and lungworms as well as the treatment of certain ectoparasitic infestations in young cattle during one grazing season, and the CVMP agreed that LONGRANGE is effective in the following indications:

Treatment of the following parasites:

- Gastrointestinal roundworms (Adult and L4): *Ostertagia ostertagi/lyrata, Cooperia oncophora/surnabada, C. punctata, Haemonchus contortus, Trichostrongylus axei, T. colubriformis, Bunostomum phlebotomum, Nematodirus helvetianus, Oesophagostomum radiatum.*
- Lungworm (Adults and L4): *Dictyocaulus viviparous;*

Prevention of reinfections with the following parasites:

- Gastrointestinal roundworms: *Ostertagia ostertagi/lyrata, Trichostrongylus colubriformis, Haemonchus contortus*, *Bunostomum phlebotomum, Oesophagostomum radiatum, Cooperia oncophora/surnabada, C. punctata, Trichostrongylus axei.*
- Lungworms: *Dictyocaulus viviparous*

Administration at the time of turnout will also treat concomitant infestations with the following ectoparasites:

Warbles (parasitic stages): *Hypoderma bovis*, *Hypoderma lineatum* Mange mites: *Sarcoptes scabiei* var*. bovis*

Sucking lice: *Linognathus vituli, Haematopinus eurysternus, Solenoptes capillatus* Horn flies: *Haematobia irritans.*

The risk for the target animal species is acceptable; however, further information and warnings would need to be included in the SPC to ensure the safe use of this product.

The risk for the user is acceptable; however, precautionary warnings would need to be added to the product information.

Regarding consumer safety, a suitable withdrawal period for edible tissues has been determined.

The use of this long acting product may be associated with an increased risk of selection of resistant helminth strains. This would have to be adequately addressed by appropriate SPC warnings and risk mitigation measures.

A major concern remains relating to the environmental safety. No appropriate measure could be determined to mitigate the risk to dung fauna associated with the use of this product. The matrix model used by the applicant to estimate the percentage of untreated animals that allow a sustained survival of yellow dung flies lacked validation with field data and the results were inconclusive and did not support the applicant's recommendation to leave 20% of the herd untreated, as a rule. The dung fauna is a complex and highly dynamic ecosystem and the lack of appropriate risk mitigation measures is considered a serious concern not only regarding the impact on dung degradation but also for the consequences on grassland insect communities, ecosystem stability and the sustainability of pasture fertility.

Therefore, in view of the serious risk to dung fauna, the CVMP considered that the data available do not allow the Committee to conclude on a positive benefit-risk balance.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for LONGRANGE is not approvable since the data on the environment, fail to demonstrate that the risks can be adequately mitigated. Therefore the data do not 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 therefore considers that the overall benefit-risk balance is negative and, therefore, recommends the refusal of the granting of the marketing authorisation for the above mentioned medicinal product.

Grounds for refusal

Whereas,

- **Grounds for refusal (environmental safety):**

  The use of LONGRANGE for cattle on pasture indicates that a serious risk for dung fauna cannot be excluded. This risk to dung fauna could not be excluded by refinement of the predicted environmental exposure concentration based on field studies with pour-on treatment as these studies were considered not representative for the intended subcutaneous use. Additionally, appropriate risk mitigation measures could not be established to mitigate the risk to dung fauna to an acceptable level.

  The risk mitigation measure proposed by the applicant to leave 20% of the herd untreated has been derived by a matrix model which is considered not reliable for the following reasons. The model has not been validated by field data, especially the crucial parameter 'adult survival rate'. Furthermore, important external parameters like emigration, predation or competition have not been considered. Additionally, the applicant's interpretation of the results that 80% herd treatment will prevent dung fly populations from extinction is highly uncertain. Therefore, it was not possible to conclude with a sufficient degree of certainty whether the risk mitigation measure to leave 20% of herd untreated is sufficiently protective in the long-term.

  In addition, it has to be considered that due to the high persistence of eprinomectin in dung and in the environment, the exposure and consequently the risk to dung fauna would also last throughout and most likely beyond the entire period of antiparasitic activity of this product.

  Therefore, CVMP considered that no appropriate risk mitigation measures can be established in line with agricultural practices to mitigate the risk to dung fauna to an acceptable level.

Therefore, the CVMP has recommended the refusal of the granting of the marketing authorisation for LONGRANGE.

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Re-examination of the CVMP opinion of 21 June 2018

Introduction

Following a negative opinion on the 21 June 2018 for Longrange, Merial requested the re-examination of the CVMP opinion under Article 34(2) of Regulation (EC) 726/2004. At the request of the applicant, an ad-hoc expert group (AHEG) meeting was held on 02 October 2018. The applicant attended the meeting to give a presentation and answer questions from the AHEG.

The applicant's grounds for re-examination, the AHEG's responses to the questions from CVMP and the CVMP final conclusions are described below.

Grounds for re-examination, AHEG and CVMP considerations

Grounds for re-examination presented by the applicant

A. The dung fly population modelling and the proposed mitigation measure were not adequately addressed

B. Procedural aspects and persistency (the applicant argued it had not been given adequate opportunity to address CVMP concerns over persistency)

C. Additional benefit of the product, being formulated with a non-PBT substance was not considered

A. The dung fly population modelling and the proposed mitigation measure

The applicant considered that the CVMP had not adequately evaluated the dung fly population model and hence the derived risk mitigation measure, to leave 20% of animals untreated, was not appropriately considered by the Committee. The applicant noted the difficulty in being able to appropriately assess and/or predict the environmental impact of eprinomectin on Yellow Dung Fly (YDF, *Scatophaga stercoraria*) or other dung fauna species, due to the complexity involved in quantifying the environmental impact of eprinomectin residues in laboratory and field settings, and highlighted that using environmental models on complex environmental systems, such as the *eprinomectin-dung-fauna-soil* system, provides practical information for evaluating potential risks, and assessing the potential impact of mitigation strategies. The applicant considers that, in view of the above, the model provided on YDF remains a suitable tool to address the long-term effects of eprinomectin on populations of dung fauna species.

Considerations on environmental modelling approaches and on the yellow dung fly population model

During the initial assessment, a population model was developed to determine the impact on dung fauna populations in farm fields, from the use of LONGRANGE in cattle. The model used YDF as a model species for the impact assessment. The applicant asserted that the findings from the population model on YDF support that leaving 20% of the cattle untreated would allow for the long-term survival of dung fauna populations. A number of uncertainties where raised by CVMP with regards to the YDF population model used, their impact on the model validation (which could not be carried out by CVMP), and hence the robustness and effectiveness of the subsequently proposed mitigation measures that would allow for the long-term survival of dung fauna species in fields where cattle are treated with LONGRANGE.

Upon re-assessment of the YDF population model by the AHEG, and consideration of its appropriateness to determine the long-term effect of LONGRANGE on dung fauna, the overall conclusion is that while the model might be suitable for determining the long-term impact of LONGRANGE on YDF populations, the parameterisation used remains unclear for most input values, as these were not provided. In addition, the

AHEG considered that the model has not been applied under a sufficient number of scenarios or for sufficient duration of time, hence compromising the validity of the results. It is also noted that the model was not made available to the CVMP or the AHEG during the procedure.

With regards to the model validation, the AHEG noted that while baseline values were compared and were in line with reported field data on YDF population values and this looks reasonable, no validation with regards to data on the effect of refugia size on the YDF population was reported (i.e., from leaving 20% of cattle untreated).

With regards to the choice of dung species used to model the long-term effects of LONGRANGE, the AHEG considered that dung species from other genera might have been more suitable model species for characterising the risks of LONGRANGE to dung fauna. Indeed, dung fauna have markedly different lifecycles, which could affect the overall toxicity profile of eprinomectin to these organisms. While YDF is the most sensitive species to eprinomectin in laboratory studies, due to its relatively high fecundity and high number of generations per year, it would be expected that recovery could be observed in the presence of relatively small refugia size. However, a larger refugia size (>20% of untreated cattle) might be needed for species that cannot reproduce as quickly, such as dung beetles. In addition, the AHEG noted that adult insects that develop with exposure to eprinomectin residues might suffer from sub-lethal effects, which may reduce longevity, mating success, fecundity, or other fitness parameters. Sub-lethal effects will vary depending on species fecundity and these should have been considered in the model.

The AHEG concluded that the YDF is not the most representative dung fauna organism for modelling the long term effects of LONGRANGE, as its life history variables make this species likely to recover faster than other dung species with lower fecundity. Ideally, a species of dung beetle (with one generation per year) should have been considered.

Considerations on the derived risk mitigation measure

The applicant proposed to include the following risk mitigation measure:

"LONGRANGE is best suited for first and second season grazing animals. Adults should not be treated with the product to ensure that a high volume of untreated dung is available to support the growth and reproduction of dung fauna during the grazing season. In any case at least 20% of the herd should be left untreated to avoid any long-term effect on the dung fauna organisms. Guidance on the selection of the untreated animals should be sought from the prescriber considering the characteristics of the herd and production system in the farm."

The CVMP concluded that there were uncertainties regarding the effectiveness of the measure to leave 20% of the herd untreated to mitigate the risks to dung fauna.

Further the CVMP acknowledges that while in certain farms adult and young cattle coexist and this measure might increase the rate of untreated animals to over 20%, this might not be the situation on all farms.

When considering the compatibility of this proposed RMM with management practices for parasite control, the AHEG concluded that the proposal for leaving 20% of animals untreated to achieve refugia for the target pathogens and to prevent anthelmintic resistance was not adequately supported. However, it was generally accepted that the provision of refugia slows the rate at which resistance occurs. The experts further added that individual farm management practices are important, and the selection/level of untreated animals might differ between farming (practices) and countries. The AHEG stated that compliance with the proposal to leave 20% untreated might also be an issue in practice; however, the CVMP acknowledged that this would be beyond the control of the applicant.

Conclusions on the grounds for re-examination: dung fly population modelling and the proposed mitigation measure

In its initial assessment, the CVMP stated that it was not possible at that time to conclude with a sufficient degree of certainty that leaving 20% of the herd untreated is an effective risk mitigation measure to protect against the long-term effects on dung fauna from the use of LONGRANGE in pasture cattle (i.e., by providing a sufficient number of dung pats with favourable conditions for survival and reproduction of dung species). The result of the re-examination in relation to the model and dung species used, confirms that the proposed risk mitigation measure of leaving 20% of the herd untreated as an effective risk mitigation measure to protect against the long-term effects on dung fauna from the use of LONGRANGE in pasture cattle, cannot be supported with confidence due to uncertainties with regards to the suitability of the species used in the model, parameterisation used, and validation of model outcome in relation to the impact of the refugia size on long term dung fauna populations.

B. Procedural aspects and persistency

The applicant has argued that the environmental persistence of eprinomectin in dung and in the environment could not be properly addressed during the authorisation procedure or oral hearing, as these concerns were only raised at the stage of the CVMP opinion. The CVMP acknowledges that the persistence of eprinomectin was not highlighted in questions put to the applicant during the procedure but notes that persistence of the substance was considered by the CVMP from the start of the procedure. For example, the persistence of the substance in different environmental compartments was noted in the environmental risk assessment included in the day 120 CVMP assessment report.

In its grounds for the re-examination the applicant goes on to present its arguments in relation to the persistence of eprinomectin in the environment.

In the initial assessment the CVMP concluded that "*due to the high persistence of eprinomectin in dung and in the environment; the exposure and consequently the risk to dung fauna would also last throughout and most likely beyond the entire period of antiparasitic activity of this product*." In the initial CVMP opinion, in reaching its conclusion the CVMP made reference to persistence in manure (with time to 50% degradation, DT_{50} of 312 - 3922 days), based on a study provided by the applicant which was conducted in accordance with OECD 307 and the EMA guideline on determining the fate of veterinary medicinal products in manure (EMA/CVMP/ERA/430327/2009). In its grounds for the re-examination the applicant stated that "*As defined within this guideline, manure may not only contain other excreta (e.g., urine), but also materials that may have been introduced during standard farming practices (e.g., spilled feed, straw, water, etc.). The characteristics of the manure (such as anaerobic conditions, pH, and temperature) used in these studies make it substantially different from dung on pasture*."

Whilst the CVMP agrees with this statement, noting that the data on degradation is based on aerobic and anaerobic degradation of chemicals in soils (OECD 307), and the guideline on determining the fate of veterinary medicinal products in manure (EMA/CVMP/ERA/430327/2009), at present no validated or standardised method for assessing the fate of VMPs in dung has been developed.

The AHEG considered whether LONGRANGE degradation in dung pats could be extrapolated from degradation studies in other matrices (manure, soil, sediment). The AHEG was of the opinion that degradation in manure cannot be used as a surrogate, and might not be directly comparable to degradation data in dung, soil or sediment. With regards to manure and dung pats, the former is collected and stored in the dark and under anaerobic conditions for weeks to months, while the latter is deposited on fields and it is not collected, but allowed to break down and degrade. In addition, they are colonised by different species of flies, beetles and worms (dung fauna are considered those species that are able to colonise pats within 2 weeks after it is deposited on the field, with timing and colonisation being

species-specific). However, the AHEG noted that while data on dung pat degradation was not available in the dossier, there is a large body of evidence from published peer reviewed data that shows that dung pats from animals treated with eprinomectin or other macrocyclic lactones significantly slow down pat degradation, and residues are detected in dung pats from treated animals for several months (for up to 4.5 months) after it is deposited in the field. While degradation of dung pats in the field is subject to several factors in addition to the activity of dung fauna (physical trampling by livestock, microbial activity, the activity of earthworms, foraging by birds, freeze/thaw cycles, the tunnelling activities of non-dung insects (ants, termites), the growth of plants through the dung pat, etc.), dung pats will degrade more quickly in the presence of insect activity. Therefore, while persistence in dung will likely not have an impact on refugia size for YDF, as these only colonise dung within two weeks after it is deposited in the field, it could affect refugia size for other soil organisms (e.g. fungivorous insects, termites, ants) delaying the overall dung pat degradation.

Overall, as dung fauna are considered to be those species that are able to colonise dung pats within 2 weeks after they have been deposited on the field, persistence of eprinomectin in dung pats beyond 2 weeks is expected to have limited additional impact on dung fauna.

The AHEG were also asked to consider if the use of such a long acting formulation and its environmental persistence may pose a long term risk to dung fauna. The AHEG considered that due to the long-lasting release of LONGRANGE into the environment, dung pats would contain residues of eprinomectin above toxic levels for the duration of the grazing season; hence colonisation of dung pats from treated animals by dung organisms would also be inhibited during that time. It was noted that for shorter lasting products, colonisation of dung pats by dung organisms might occur at a later stage of the grazing season due to the shorter duration of excretion.

Conclusions on the grounds for re-examination regarding procedural aspects and persistency

The CVMP acknowledges that dung organisms are considered those species that are able to colonise dung within two weeks from a dung pat being deposited in the field. Hence, any persistence of eprinomectin residues in dung pats after 2 weeks will not pose an additional risk for the dung fauna. The AHEG highlighted, however, that the continuous release of eprinomectin residues in the excreted dung throughout, and most likely beyond the entire period of antiparasitic activity of this product, with concentrations above those established to have a toxic effect to dung organisms will prevent colonisation of pats by dung fauna.

C. Additional benefit of the product, being formulated with a non-PBT substance

The applicant highlighted the relative merits of eprinomectin as not fitting the characterisation criteria for a PBT substance. While not being a PBT, eprinomectin is classified as very persistent (vP) and toxic according to the criteria used to characterize PBT substances (see the CVMP guideline on the assessment of PBT substances in VMPs, EMA/CVMP/ERA/52740/2012). The CVMP notes that the data indicates that LONGRANGE shows an effect to dung fauna lasting over the entire period of antiparasitic activity of this product and there are limited or no appropriate risk mitigation measures, in line with agricultural practices available to mitigate this risk to an acceptable level. The CVMP is of the opinion that the fact that eprinomectin is not classified as a PBT substance cannot be considered a benefit of the product, particularly in light of the fact that comparative assessments are not carried out within the current legislative framework as part of the authorisation process.

Conclusions on the grounds for re-examination with regards to the benefit of the product, being formulated with a non-PBT substance

The CVMP concludes that in the case of this evaluation eprinomectin being a non PBT substance is not considered a benefit of the product.

Final benefit-risk assessment further to re-examination

Introduction

LONGRANGE 50 mg/ml is a prolonged-release formulation containing eprinomectin as the active ingredient and is intended for the treatment of gastrointestinal nematode and lungworm infections, warbles (parasitic stages), mange mites, lice and horn flies, and for the prevention of re-infestations with certain gastrointestinal nematode species and lungworms for up to 120 days. The proposed treatment dose is a single subcutaneous dose of 1 mg/kg bw (1 ml/50 kg) to be administered at the back of the ear. The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application).

Benefit assessment

Direct therapeutic benefit

The proposed benefit of LONGRANGE includes its immediate efficacy in the treatment of infestations with gastrointestinal nematodes and lungworms, and ectoparasites (warbles (parasitic stages), mange mites, lice and horn flies), and its persistent effect in the prevention of reinfections with certain gastrointestinal nematode species and lungworms for up to 120 days after treatment.

The proposed indications were investigated in a large number of well-designed laboratory and field studies in young cattle, (mainly beef but also dairy calves) which were, in general, conducted to current scientific standards. However, most of these studies have been conducted with the product authorised in the USA and Canada with a different site of the subcutaneous injection (subcutaneous injection in the shoulder), while the back of the ear is the intended site of injection for the EU LONGRANGE product. Efficacy rates in these studies were well above the threshold recommended in the VICH guidelines.

From the data provided, the immediate (therapeutic) efficacy of LONGRANGE in the treatment of the claimed endo- and ectoparasites (gastrointestinal nematodes and lung worms, warbles, mange mites, lice, and horn flies) could be accepted, as the applicant demonstrated sufficiently similar initial eprinomectin plasma concentrations after injection, either in the shoulder or at the back of the ear. The claimed persistent effect, i.e. prevention of reinfection with certain gastrointestinal nematodes and lungworms has been demonstrated for up to day 100 or 120, depending on the target parasite species.

Additional benefits

LONGRANGE is a prolonged-release formulation that is expected to be administered only once a year at the start of the grazing season, and would therefore reduce the need for repeated antiparasitic treatments of cattle on pasture.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate 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. In general, the dossier takes into account current rules and guidelines. There are no major objections on the quality part of the dossier.

Safety

Risks for the target animal:

In the absence of data, calves younger than 3 months should not be treated with this product.

Adverse reactions comprise of swelling, heat and pain at the injection site, which occur very commonly and resolve without intervention within 4-6 weeks.

As no data is available to assess fertility and reproduction parameters after eprinomectin treatment in male cattle, bulls intended for breeding should not be treated with this product.

As the reproductive safety of the product has not been established before 10 weeks after administration, it is not recommended to treat pregnant animals or to breed animals before that time.

Since no data demonstrating persistent efficacy and a margin of safety has been provided in that subgroup, lactating cattle were removed from the proposed product information.

Special risks

The use of this long acting product may be associated with an increased risk of selection of resistant helminth strains. The applicant's recommendation to leave 20% of the animals in a herd untreated, as a rule, was mainly derived from a matrix modelling approach to predict the potential long-term impact on dung fauna, but no data have been made available to demonstrate the efficacy of this systematic approach in reducing the selection of resistant nematodes.

Risk for the user

A mostly appropriate user safety assessment has been provided. User safety risks have been identified, which are mainly associated with accidental self-injection, but also with accidental eye and dermal contact. However, RMMs regarding hypersensitivity and developmental toxicity have not been addressed sufficiently in the product literature.

Risk for the environment

A risk was identified for the sediment compartment and for dung fauna. The risk to sediment could be reduced by keeping treated cattle away from lakes and streams for three weeks after treatment and through the inclusion of corresponding advice in the product literature. However, a risk to dung fauna is indicated due to the long excretion duration of eprinomectin that could prevent recovery of the dung fauna populations on pastures used by treated animals. The proposed risk mitigation measure to leave 20% of the herd untreated, based on population modelling for the yellow dung fly (*Scatophaga stercoraria*) is not substantiated by the model with a sufficient degree of certainty on whether the risk mitigation measure is sufficiently protective for dung insects in the long-term. Additionally, it has to be considered that the persistence of eprinomectin in the environment as a result of the release of dung pats containing residues of eprinomectin above toxic levels over and most likely beyond the entire period of persistent antiparasitic activity of this product, will result in a long term risk to dung fauna.

Therefore, CVMP concludes that the long term risk to dung fauna cannot be considered to be mitigated based on the data provided.

Risk for the consumer

Eprinomectin has been evaluated previously in respect to the safety of residues and MRLs have been established for target species and food commodities concerned under this application.

A withdrawal period of 106 days for edible tissues from treated cattle was considered necessary to ensure consumer safety. The product is not proposed for use in lactating animals.

Risk management or mitigation measures

Information relating to potential risks of this product relevant to the target animal would need to be supplemented in the product literature if authorised in order to prevent or reduce potential risks in pregnant and breeding animals.

Based on the data presented it was agreed to mention in the product literature that no reproductive safety studies have been conducted with the product when administered as intended and that it is therefore not recommended to treat pregnant animals and to breed animals before 10 weeks after administration.

In order to minimise the potential risk for the development of resistant helminths, appropriate risk mitigation measures would need to be implemented. This should include a targeted selective treatment concept, where a number of animals in a herd would be left untreated to maintain a susceptible worm population on pasture. The decision on how many animals would need to be left untreated would be made by the responsible veterinarian on the farm, taking into account local epidemiological, clinical and parasitological aspects.

Regarding user safety, warning phrases would need to be supplemented in the SPC and other product information, if authorised, in order to protect persons with known hypersensitivity to product ingredients as well as women intending to become pregnant, those who are pregnant and those that are breastfeeding.

Regarding consumer safety, a suitable withdrawal period for edible tissues was agreed.

Regarding the environment, suitable information for inclusion in the SPC and other product information were agreed regarding potential risks for aquatic ecosystems and advice on how to prevent or reduce these risks. No appropriate risk mitigation measures could be established to address the long term risk for dung fauna based on the data presented.

Evaluation of the benefit-risk balance

Information on development, manufacture and control of the active substance and finished product has been presented and led to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The product has been shown to be efficacious in the control of infections with gastro-intestinal nematodes and lungworms as well as the treatment of certain ectoparasitic infestations in young cattle during one grazing season, and the CVMP agreed that LONGRANGE is effective in the following indications:

Treatment of the following parasites:

- Gastrointestinal roundworms (Adult and L4): *Ostertagia ostertagi/lyrata, Cooperia oncophora/surnabada, C. punctata, Haemonchus contortus, Trichostrongylus axei, T. colubriformis, Bunostomum phlebotomum, Nematodirus helvetianus, Oesophagostomum radiatum.*
- Lungworm (Adults and L4): *Dictyocaulus viviparous;*

Prevention of reinfections with the following parasites:

- Gastrointestinal roundworms: *Ostertagia ostertagi/lyrata, Trichostrongylus colubriformis, Haemonchus contortus*, *Bunostomum phlebotomum, Oesophagostomum radiatum, Cooperia oncophora/surnabada, C. punctate, Trichostrongylus axei.*
- Lungworms: *Dictyocaulus viviparous*

Administration at the time of turnout will also treat concomitant infestations with the following ectoparasites:

Warbles (parasitic stages): *Hypoderma bovis*, *Hypoderma lineatum* Mange mites: *Sarcoptes scabiei* var*. bovis*

Sucking lice: *Linognathus vituli, Haematopinus eurysternus, Solenoptes capillatus* Horn flies: *Haematobia irritans.*

The risk for the target animal species is acceptable; however, further information and warnings would need to be included in the SPC to ensure the safe use of this product.

The risk for the user is acceptable; however, precautionary warnings would need to be added to the product information.

Regarding consumer safety, a suitable withdrawal period for edible tissues has been determined.

The use of this long acting product may be associated with an increased risk of selection of resistant helminth strains. This would have to be adequately addressed by appropriate SPC warnings and risk mitigation measures.

A major concern remains relating to the environmental safety. No appropriate measure could be determined to mitigate the risk to dung fauna associated with the use of this product. The matrix model used by the applicant to estimate the percentage of untreated animals that allow a sustained and long term survival of yellow dung flies lacked validation with field data and the results were inconclusive and did not support the applicant's recommendation to leave 20% of the herd untreated.

The dung fauna is a complex and highly dynamic ecosystem and the lack of appropriate risk mitigation measures is considered a serious concern not only regarding the impact on dung degradation but also for the consequences on grassland insect communities, ecosystem stability and the sustainability of pasture fertility.

The AHEG agreed with the original findings of the CVMP. They considered that the figure of 20% is not supported by the modelled data, and the model outputs do not appear to be sufficiently validated. They also thought it doubtful that YDF is a worst case representation of the dung fauna considering its high fecundity, which would allow a faster recovery in comparison with other dung fauna (e.g. dung beetles).

Therefore, in view of the serious long-term risk to dung fauna, the CVMP considered that the data available do not allow the Committee to conclude on a positive benefit-risk balance.

Conclusion (further to re-examination)

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for LONGRANGE is not approvable since the data on environmental safety fail to demonstrate that the risks can be adequately mitigated. Therefore the data do not 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 therefore considers that the overall benefit-risk balance is negative and, therefore, recommends the refusal of the granting of the marketing authorisation for the above mentioned veterinary medicinal product.

Grounds for refusal

- **Grounds for refusal (environmental safety)**

The use of LONGRANGE for cattle on pasture indicates that a serious long-term risk for dung fauna cannot be excluded. This risk to dung fauna could not be excluded by refinement of the predicted environmental exposure concentration based on field studies with pour-on treatment as these studies were considered not representative for the intended subcutaneous use. Additionally, appropriate measures could not be established to mitigate the risk to dung fauna to an acceptable level.

The risk mitigation measure proposed by the applicant to leave 20% of the herd untreated has been derived by a matrix model which is considered not reliable for the following reasons; the model has not been validated by field data, especially the crucial parameter 'adult survival rate'. Furthermore, important external parameters like emigration, predation or competition have not been considered. In addition, the model does not include considerations on possible sub-lethal effects or the effects on different climatic or multi-generational scenarios and it is not certain that the YDF is a worst case representative of dung fauna. Therefore, it was not possible to conclude with a sufficient degree of certainty whether the risk mitigation measure to leave 20% of the herd untreated is sufficiently protective in the long term considering the persistence of eprinomectin in the environment as a result of the release of dung pats containing residues of eprinomectin above toxic levels lasting over and most likely beyond the entire period of persistent anti-parasitic activity of this product.

Therefore, the CVMP has recommended the refusal of the granting of the marketing authorisation for LONGRANGE during their meeting on 6 – 8 October 2018.