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Committee for Medicinal Products for Veterinary Use

CVMP assessment report for GALLIPRANT (EMEA/V/C/004222/0000)

International non-proprietary name: grapiprant

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

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Introduction

The applicant Aratana Therapeutics NV submitted on 26 January 2016 an application for a marketing authorisation to the European Medicines Agency (The Agency) for GALLIPRANT, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 7 May 2015 as GALLIPRANT contains a new active substance (grapiprant) which was not authorised as a veterinary medicinal product in the Union on the date of entry into force of Regulation (EC) No 726/2004.

The applicant applied for the following indication: For the treatment of pain and inflammation associated with osteoarthritis in dogs.

The active substance in GALLIPRANT is grapiprant, a non-steroidal, non-cyclooxygenase inhibiting anti-inflammatory drug in the piprant class. Grapiprant is a selective antagonist of the prostaglandin E_2 EP_4 receptor, resulting in a reduction of pain and inflammation. The target species is dog.

GALLIPRANT is presented in tablets of 20, 60 or 100 mg of grapiprant in a bottle containing 7 or 30 tablets.

The applicant (Aratana Therapeutics NV) is registered as an SME pursuant to the definition set out in Commission Recommendation 2003/361/EC; however, the applicant out-licensed their application for GALLIPRANT to Elanco on 22 April 2016.

The rapporteur appointed is Keith Baptiste 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.

On 9 November 2017, the CVMP adopted an opinion and CVMP assessment report.

On 9 January 2018, the European Commission adopted a Commission Decision granting the marketing authorisation for GALLIPRANT.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated 13 January 2016 and revised 2 June 2017), which fulfils requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Manufacture of the dosage form, quality control and packaging takes place outside the EEA. A satisfactory certificate of GMP compliance of the site has been issued by the competent authority of New Zealand. As there is a mutual recognition agreement in place for Good Manufacturing Practice (GMP) between the EU and New Zealand, the site was considered appropriately certified as complying with GMP requirements.

Batch release takes place at Klifovet AG, Munich, Germany, which holds a manufacturing and import authorisation (MIA) issued by Regierung von Oberbayern/Germany.

A satisfactory QP declaration has been submitted and signed by the qualified person at Klifovet AG, Germany, responsible for EU batch release, declaring that the active substance is being manufactured in accordance with GMP for starting materials.

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 is in line with the legal requirements.

Part 2 - Quality

Composition

The finished product is presented as immediate release tablets for oral use containing 20 mg, 60 mg or 100 mg grapiprant as the active substance.

Other ingredients are: Spray dried pork liver powder EHT (flavouring), lactose monohydrate (diluent), sodium starch glycolate Type A (disintegrant), sodium laurilsulfate (wetting agent), copovidone (binder), cellulose microcrystalline (binder and diluent), magnesium stearate (lubricant) and silica colloidal anhydrous (glidant).

All the excipients are listed in section 6.1 of SPC.

Containers

The product is packaged in induction sealed, white, round high density polyethylene bottles (20, 35 and 60 ml) with a threaded child-resistant cap with rayon coil. The applicant initially proposed a pack size of 7, 30 or 90 tablets per bottle; the 90 tablets presentation was, however, withdrawn during the

procedure. The materials comply with the relevant European Pharmacopoeia (Ph. Eur.) or EU legislation for materials intended to come into contact with food. The choice of the container closure system has been validated by stability data and was demonstrated to be acceptable for the intended use of the product.

Development pharmaceutics

The development of the drug product was described with respect to the choice of formulation and manufacturing process. Apart from the excipient used for flavouring (spray dried pork liver powder EHT), all excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards.

A study has been presented on content uniformity of split tablets, which is considered equivalent to the test for Subdivision of tablets by mass described in the Ph. Eur. monograph. The data provided shows that all three tablet strengths can be split without any significant adverse effects with respect to loss of mass, content uniformity, friability or disintegration time. It has been demonstrated that the tablets can be divided into two equal halves.

Method of manufacture

The different tablet strengths are manufactured from a common blend using a standard process of direct compression. The manufacturing process, in-process controls and production batch sizes are adequately described. Process validation schemes have been provided for the production scale batch size of tablet blend.

Control of starting materials

Active substance

The active substance grapiprant is a white to off-white crystalline powder with polymorphic form A. The active substance is readily soluble in water. Nineteen polymorphic forms have been identified and the active substance specification contains a test for polymorphic Form A by XRPD. The characterisation of the active substance and its impurities is in accordance with the CVMP guideline on chemistry of new active substances (EMEA/CVMP/541/03/Final). The active substance is manufactured by chemical synthesis.

The manufacturing process and in-process controls have been adequately described. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The active substance specification includes tests for appearance, identity, assay, impurities, water content, residue on ignition, heavy metals, polymorphic form A, residual solvents, and particle size distribution . The analytical methods used have been adequately described and validated. The information regarding the active substance reference standard is satisfactory. Batch analysis data for the active substance have been provided for three commercial scale batches demonstrating compliance with the specification.

A re-test period for the active substance of 24 months when stored in HPDE drums lined with two clear polyethylene bags has been proposed. Stability data for the active substance stored in packaging simulating normal bulk storage conditions have been provided for 24 months at 25 °C/60% RH and 6 months at 40 °C/75% RH according to the VICH GL3 on stability testing of new veterinary drug substances and medicinal products. The parameters tested are the same as in the active substance specification. All results comply with the proposed specification and no trends are observed.

Photostability testing following the VICH guideline GL5 show that the active substance is not light sensitive. The proposed re-test period/storage conditions are approved.

The finished product manufacturer's specification and test methods are the same as used by the active substance manufacturer. Batch analysis data issued by the finished product manufacturer have been provided for the active substance.

Excipients

Apart from the spray-dried pork liver powder EHT, all excipients comply with the relevant Ph. Eur. Monograph, and the additional requirements for residual solvents for the excipients sodium starch glycolate Type A and copovidone. For the excipient spray-dried pork liver powder EHT, the manufacturing process is described briefly and specifications as well as a certificate of analysis (CoA) are presented.

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

The only materials of animal origin used in the product are lactose and spray dried pork liver powder. For lactose, compliance with the Note for Guidance (EMA/410/01 rev 3) is stated. Since the excipient spray dried pork liver powder is derived from pigs, it is not relevant with respect to TSE.

Control tests on the finished product

The specifications proposed for use at release and at the end of shelf-life include appropriate parameters and are as follows: appearance, identification, uniformity of weight, hardness, loss on drying, friability, disintegration, uniformity of dosage units, assay, related substances, dissolution and microbiological quality . The analytical methods used have been adequately described and validated. Batch analysis data for the finished product are provided for eleven batches covering the three strengths. The test results confirm the consistency of the manufacturing process.

Stability

Stability data of eight batches of finished product covering the three strengths in the three packaging configurations initially proposed (7, 30 or 90 tablets per bottle) have been presented. The bottle containing 90 tablets has, however, been removed from the application during the procedure. The bottles were stored for 36 months at 30 °C/65% RH and for 6 months at 40 °C/75% RH. At 30 °C/65% RH, all results comply with the shelf-life specification, but at 40 °C/75% RH out of specification results are observed.

In addition, one batch of drug product was exposed to light according to the VICH GL5 and it has been demonstrated that the drug product is photo stable. Furthermore, an in-use stability study for half tablets was conducted at 25 °C/60% RH up to 90 days. All results comply with the shelf-life specification. Additional in-use stability testing will be performed post-approval.

The following shelf-life/storage conditions are considered acceptable: 3 years/ Store below 30 °C. In-use shelf-life for whole and half tablets of 3 months.

Overall conclusions on quality

The quality of GALLIPRANT 20 mg, 60 mg and 100 mg tablets has been demonstrated to meet current European regulatory requirements.

Active substance

The description of the manufacturing process, controls of starting materials and reagents and the discussion and control of impurities are acceptable. The provided specifications for the drug substance product are acceptable.

Stability studies have been performed with the drug substance. A re-test period of 24 months when stored in HPDE drums lined with two clear polyethylene bag is acceptable.

Active substance – finished product manufacturer

The finished product manufacturer's specification and test methods of the active substance are the same as those used by the active substance manufacturer.

Finished product

The development of the product has been described, the choice of excipients and their functions explained.

The manufacturing process and in-process controls are described adequately. Process validation schemes have been provided for the production scale batch size.

The product specifications cover the appropriate parameters for this dosage form and the acceptance criteria are justified. The methods have been described and validated. Batch analysis has been performed and the results show that the finished products meet the specifications proposed.

Stability data at 30 °C/65% RH, 40 °C/75% RH, photostability data and in-use data at 25 °C/60% RH for half tablets have been presented. The following shelf-life/storage conditions are considered acceptable: "3 years. Store below 30 °C. In-use shelf-life for whole and half tablets of 3 months."

Recommendations

The applicant is recommended to perform additional in-use stability testing post-approval.

Part 3 – Safety

The active substance of GALLIPRANT is grapiprant, an analgesic and anti-inflammatory drug, non-steroidal, non-cyclo-oxygenase inhibitor of the piprant class that functions as a selective antagonist of the EP_4 receptor. Grapiprant is a new active substance not authorised previously as a veterinary medicinal product in the EU. A full safety file in accordance with Article 12(3)(j) has been provided.

Pharmacodynamics

Please refer to Part 4.

Pharmacokinetics

Please refer to Part 4.

Toxicological studies

Two single-dose and eight repeated dose oral toxicity studies were provided.

Single dose toxicity

Acute oral toxicity was evaluated in rats and dogs applying doses of 250, 500, 1000 or 2000 mg/kg bw to rats and 100, 300 or 1000 mg/kg bw to dogs in 0.5% methylcellulose suspension by gavage. Although the studies - originating from 2003 - were not performed according to the current OECD Guideline 420, the most relevant toxicological aspects were evaluated.

Single dose toxicity after oral administration was low, particularly in rats. Thus, in rats no mortality was seen in any of the doses. At 2000 mg/kg bw a decrease in body weight was observed. It was concluded that the No Observed Adverse Effect Level (NOAEL) for single dose oral toxicity was 1000 mg/kg bw.

In dogs, a (NOAEL) could not be determined as some milder clinical signs (e.g. emesis, loose and mucous faeces and cardiovascular changes) were observed at every dose tested, including the lowest dose (100 mg/kg bw). Effects increased in frequency and severity at a dose of 1000 mg/kg bw, estimated to be the minimum lethal dose.

Repeat dose toxicity

Repeat dose toxicity studies were carried out in rats, mice, and dogs. The pivotal one-month studies in rats and mice and the 9-month study in dogs were GLP compliant.

In repeat-dose toxicity studies in rats, mice and dogs, animals were treated once daily by oral gavage for durations of 10 days to 9 months at grapiprant doses of up to 2000 mg/kg bw/day. The main findings were gastrointestinal effects, which increased in severity with increasing dose, and cardiovascular effects in dogs were noted at doses higher than 50 mg/kg bw/day. At high dose levels, changes were observed in serum chemistry (e.g. decreases in total protein, albumin, globulin and calcium) in all species, and in haematology (e.g. decrease in red blood cells and haematocrit) parameters in rodents. These haematology changes were considered to be secondary to the gastrointestinal effects resulting from grapiprant's pharmacology, which at high doses in rodents can lead to erosion/ulceration of the gut epithelium causing gastrointestinal blood loss.

The NOAEL in rats and mice in the one-month repeated dose studies were 400 mg/kg bw and 100 mg/kg bw, respectively. Changes observed at these dose levels are concluded as follows. Gross lesions observed in the stomach from the 1-month repeat dose oral toxicity study, as well as the findings of cellular infiltrations in rodent stomachs from the 2-week oral toxicity study in mice, were not dose-related and not related to adverse findings. It is accepted that the observed findings were of a mild nature and not dose-related.

The repeated dose toxicity studies in dogs are addressed in Part 4.

Tolerance in the target species of animal

Please refer to Part 4.

Reproductive toxicity

Studies on developmental and reproductive toxicity were not performed with grapiprant. Limited data could be gained from the pivotal target animal safety study in which no treatment-related changes in reproductive organ weights or other adverse effects on reproductive organs were observed.

Considering that the product is expected to be used mostly in older dogs, the lack of specific reprotoxicity data is acceptable; however, the use of the product is contraindicated in pregnant and lactating dogs as well as in breeding animals.

Genotoxicity

The genetic toxicology potential of grapiprant was evaluated in a standard test battery in accordance with VICH guideline GL23.

For the Ames test, grapiprant was negative for induction of reverse mutations in the tester strains of *Salmonella typhimurium* (four strains) and *E. coli* (one strain) as well as in the presence and absence of metabolic activation.

Grapiprant did not induce chromosomal aberration *in vitro* in lymphocytes in the presence of a rat liver metabolic activation system after three hours testing. Under 24 hour direct testing conditions, grapiprant produced a dose-related and statistically significant increase in chromosome damage (up to 23.3% abnormal cells) compared to the negative control (DMSO; 2.0% abnormal cells). However, the findings of the 24 hour chromosomal aberration test, under direct test conditions, were not considered an indication of *in vivo* genotoxicity since all other tests were negative.

For the *in vivo* micronucleus test in rats, grapiprant did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of rats treated for two consecutive days at oral doses of 0, 500, 1000 or 2000 mg/kg bw.

Based on the above studies, it was concluded that grapiprant is not genotoxic.

Carcinogenicity

No carcinogenicity data have been provided. This is considered acceptable due to the lack of genotoxic potential, the lack of structural alerts, and the lack of findings relevant to neoplastic lesions in repeat dose toxicity studies.

Studies of other effects

Grapiprant did not show skin irritation nor skin corrosion properties in studies performed according to OECD *in vitro* test guidelines. Assessment of contact hypersensitivity to grapiprant was carried out in a mouse local lymph-node assay. Based on these study results, grapiprant is not regarded as a skin sensitizer. An eye irritation study performed *in vitro* on bovine cornea did not reveal eye irritation for the product GALLIPRANT.

Trials in humans (three phase 1 trials in healthy volunteers, and one phase 2a in adults with osteoarthritis in the knee) were conducted as part of the human drug development program. In these studies, grapiprant was administered as single doses of 1 to 2000 mg/person or as a twice daily dose of 50 to 300 mg/person over a 14-day period. Grapiprant was generally well-tolerated and adverse events were mild in intensity and reported as abdominal pain, chest pain, nausea and GI effects. The incidence of GI effects increased with increasing dose following repeated administration of 50 and 250 mg/person twice daily. Serious individual adverse events were reported after administration of a single dose of 1500 mg/person (e.g. elevated serum creatinine and blood urea nitrogen) and after administration of repeated doses of 150 mg/person (e.g. decreased haemoglobin and haematocrit as well as gastrointestinal haemorrhage).

No studies were conducted for antimicrobial activity, although grapiprant is a sulphonamide derivative. However, the substance is not expected to have antimicrobial activity due to its chemical structure.

Excipients

The excipients of the product GALLIPRANT are well known for use in veterinary medicine. Their use does not raise any specific concerns.

User safety

A user risk assessment was carried out according to the CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-FINAL-Rev.1), taking into account likely routes of exposure (dermal, inhalation, ocular, hand-to-mouth, oral) and users (professional and non-professional, including children). The exposure to the active ingredient via the most likely route (hand-to-mouth contact when dividing the tablets) was considered to be minimal.

The most severe risk was accidental ingestion of the tablet, with the highest strength, by a child. The applicant calculated the exposure as 6.13 mg/kg bw based on a 100 mg tablet and a 16.3 kg child. The dose was compared to the dose tolerated by humans, where a single dose of 16.7 mg/kg bw was generally well tolerated in a clinical phase 1 trial. However, the calculated exposure should be compared to a no effect dose. Adverse events were reported at dose levels lower than 16.7 mg/kg bw in healthy volunteers, and 0.8 mg/kg bw twice per day was pharmacologically active in patients. In addition, in-line with the examples provided in the CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/2003 Rev. 1), a body weight of 10 kg should be assumed for children. Therefore the applicant provided a new exposure calculation and re-considered the exposure in relation to an appropriate reference value for "no concern". Although the margin of exposure is lower than 100, sufficient mitigation measures are in place: an adequate warning is stated in the SPC and the product is marketed in child-resistant packages.

No developmental and reproductive toxicological data were provided, and a contraindication to use the product in pregnant animals has been included. Furthermore, the human exposure by handling the product is expected to be very low. Therefore, a SPC warning for pregnant women or women of child-bearing age was not considered necessary.

Environmental risk assessment

An environmental risk assessment (ERA) was provided according to the Guideline on environmental impact assessment (EIAS) for veterinary medicinal products – Phase I (CVMP/VICH/592/98-FINAL). The environmental risk assessment can stop in Phase I as the product will be used only in non-food producing animals. Standard advice for waste disposal is included in the SPC.

GALLIPRANT is not expected to pose a risk to the environment when used according to the SPC.

Overall conclusions on the safety documentation

Toxicology

Grapiprant is of low acute toxicity after oral dosing in rats and dogs.

In repeated-dose studies the NOAEL in rats and mice were 400 mg/kg bw and 100 mg/kg bw respectively after one month dosing. The main findings were gastrointestinal effects, whose severity increased with increasing dose. At high dose levels, changes were also observed in serum chemistry (e.g. decreases in total protein, albumin, globulin and calcium) in all species, and in haematology (e.g. decrease in red blood cells and haematocrit) parameters in rodents. The applicant stated that the NOAEL for dogs was 6 mg/kg bw concluded from the 1-month and 9-month repeat dose oral safety studies. This was accepted by CVMP.

Based on negative results from the Ames test, the *in-vitro* chromosomal aberration test in the presence of metabolic activation after 3 hours and 24 hours, the 3 hour *in-vitro* chromosomal aberration test without metabolic activation and the two *in-vivo* studies (rat micronucleus assay and

rat primary hepatocyte cultures), grapiprant is not considered genotoxic. Carcinogenicity studies have not been performed and were not requested.

The substance was shown to be non-irritant to skin, a non-sensitizer of skin and the product did not cause eye-irritation.

The data presented are considered adequate to characterise the toxicity profile of the active substance, with the exception of reproductive toxicity effects, where no data were submitted. Considering, that the product is expected to be used mostly in older dogs, the omission is acceptable. However, grapiprant use in pregnant and lactating bitches as well as in breeding animals is contraindicated.

User safety

A user safety assessment has been presented. The worst-case senario was considered to be accidental ingestion of the tablet, with the highest strength, by a child. Appropriate warning is stated in the SPC and the product is intended to be marketed in child-resistant packages.

Despite the absence of any developmental and reproductive toxicological data, exposure of pregnant women or women of child-bearing age is expected to be low, and a SPC warning is therefore not considered necessary.

Environmental safety

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

In conclusion, the product is considered to have low toxicity.

Part 4 – Efficacy

GALLIPRANT was proposed by the applicant to be used for the treatment of pain and inflammation associated with osteoarthritis in dogs at a proposed oral dose of 2 mg/kg bw administered once daily.

The preclinical data package included a series of *in vitro* and *in vivo* studies covering the pharmacodynamic and pharmacokinetic characteristics of grapiprant as well as three laboratory studies in dogs addressing target animal safety. Three clinical and pharmacology studies in humans were provided for the purpose of dose extrapolation to dogs. Two field studies were presented to confirm that the extrapolated dose of 2 mg/kg bw demonstrated clinical effects in the target population. Safety data were also obtained from these studies.

The applicant followed the principles of the requirements outlined in the Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMA/CVMP/EWP/1061/2001) in most parts of the efficacy documentation, except those concerning dose determination.

Pharmacodynamics

GALLIPRANT (active ingredient grapiprant) is a new analgesic and anti-inflammatory drug, non-steroidal, non-cyclo-oxygenase inhibitor of the piprant class that functions as a selective antagonist of the EP_4 receptor. The EP_4 receptor is the primary mediator of the prostaglandin E_2 (PGE_2) elicited sensitization of sensory neurons. Furthermore, EP_4 receptor is expressed in a variety of other tissues and cells, including the osteoarticular, immune, cardiovascular, gastrointestinal and respiratory systems.

A series of *in vitro* studies were provided to investigate the antagonist activity to EP_4 receptors and binding affinity of grapiprant to EP_4 receptors of humans, rats and/or dogs.

Nine *in vivo* studies were provided to assess the pharmacodynamics of grapiprant in various rodent pain and inflammation models. Results of these studies showed that PGE_2 is a clinical mediator of pain and inflammation, and that grapiprant was able to block PGE_2-elicited pain and inflammation by blocking the EP_4 receptor. The calculated minimum effective dose (MED) in these studies to achieve pain control in rats ranged from 19 to 133 mg/kg bw.

Eight *in vivo* studies and three *in vitro* studies were submitted for the evaluation of the secondary pharmacological effects of grapiprant on various organ systems of dogs and rats. Main organ systems that were investigated were the cardiovascular and neurological system, also including renal and haemodynamics. Administration of grapiprant showed no neuronal or cardiovascular pharmacodynamic action at doses of 3, 10, and 30 mg/kg, suggesting that such effects should not be expected at therapeutic doses of GALLIPRANT in dogs. Only at very high doses of 100 mg/kg bw and 300 mg/kg bw resulted with increases in heart rate. Also, cardiovascular effects (variable increases in cardiac QTc interval and increased heart rate) were seen in the single dose acute toxicity study in dogs (at doses of 100, 300 and 1000 mg/kg bw).

The applicant put forward the hypothesis that the mode of action of grapiprant (selectively inhibiting the EP_4 subclass of receptors) would improve the tolerance compared to other NSAIDs by sparing the activities that are mediated through EP_1, EP_2, EP_3, prostacyclin (PGI_2) and thromboxane A_2 receptors. Based on a literature review, the applicant showed that by selectively targeting the EP_4 receptor, certain processes are less or not affected by grapiprant compared to other NSAIDs, including renal function, clotting, gastric ulceration, and fever reduction.

In conclusion, primary and secondary pharmacodynamics of grapiprant are documented and have been evaluated satisfactorily in dogs. *In vitro* studies assessing the antagonist activity of grapiprant on EP_4 receptors, expressed in HEK293 cells, were done on rat and human cell lines, only.

Pharmacokinetics

Two *in vitro* and twelve *in vivo* pharmacokinetic studies were performed to determine the pattern of absorption, distribution, metabolism and excretion of grapiprant in dogs.

Grapiprant is rapidly absorbed from the gastrointestinal tract. The rate of absorption is affected (i.e. delayed) by feeding. Thus, the time of peak concentration, T_{max} is seen normally within one hour after application of the tablet formulation in the fasted state whereas it is 2.5 hours after administration of the tablet in the fed state.

Oral bioavailability is approximately 90% when given to fasted dogs. Feeding has a negative effect on oral bioavailability, since the geometric mean ratios (fed/fasted) for the AUC and C_{max} were 37% and 20% respectively.

Grapiprant is highly protein bound (95%). The volume-of-distribution was 0.79 l/kg, indicating an almost equal distribution between blood and tissue. There were no indications of accumulation of the drug during longer-term treatment.

Grapiprant is metabolised into three different metabolites by N-deamination, hydroxylation or N-oxidation, but mainly excreted as unchanged drug. The main route of excretion is biliary and total faecal excretion accounts for 65% of the dose. Urinary excretion accounts for 20% of the excreted drug.

The elimination half-life of grapiprant is approximately 4.6 to 5.7 hours.

Dose justification

The proposed dose of 2 mg grapiprant/kg bw once daily in dogs was initially based on an extrapolation calculation from the minimum effective dose established from clinical trials in human medicines development (see *studies of other effects*).

Based on clinical trials in humans, a therapeutic (human) dose of 2 x 50 mg/person/day was selected. Considering the short half-life of grapiprant (approximately 6-7 hours), the demonstration of linear kinetics for AUC, and little to no accumulation of grapiprant in healthy persons at this dose, the corresponding AUC in humans, as reported after administration of a single 100 mg dose (7220 ng*h/ml), was used as a basis to obtain a corresponding efficacious AUC (AUC_{eff}) for dogs. Thus, the human AUC was corrected using the receptor binding affinity and the unbound drug fraction in humans and dogs, giving an AUC_{eff} in dogs of 2726 ng*h/ml. A corresponding single dose of 2 mg/kg bw was estimated, based on a canine pharmacokinetic study (study AT001-CPK-12-009) in which a single dose of 2 mg/kg bw of the final formulation of GALLIPRANT was administered to healthy fasted Beagle dogs.

A comparable AUC_{eff} value, leading to approximately the same canine dose of 2 mg/kg, could also be calculated based on the highest minimum effective dose seen in rat pain and inflammation models (133 mg/kg bw).

However, the CVMP noted that more than one dose per day, as applied in many human and rat studies, may be necessary to maintain an effect: this was taken into account in the pre-clinical dose selection process. Also, some questions remained open related to the reference(s) and the formula used to extrapolate the AUC_{eff} from humans to dogs. Overall, the CVMP considered that the dose justification was not fully supported, but was accepted in view of the results from the canine clinical studies.

Dose determination/confirmation studies

Four non-GLP exploratory efficacy studies in canine experimental models of osteoarthritis were conducted. Efficacy of grapiprant was tested at doses of 1 mg/kg, 2 mg/kg, 3 mg/kg, 10 mg/kg and 30 mg/kg bw against a positive control (firocoxib) and/or a negative control. Three of these studies were performed in Beagle dogs with meniscal release of the stifle joint. The efficacy evaluation consisted of a kinetic assessment, lameness assessment and orthopaedic assessment. Statistically significant improvements were only seen in single parameters at single time points and no increase in efficacy was seen at increasing doses of grapiprant. Some improvement was found for the positive control in one of the studies. However, due to deficiencies in the disease model, study design and insufficient numbers of animals, the applicant regarded these studies as proof-of-concept only.

In addition to these studies, the applicant also conducted a dose finding/confirmation study under field conditions, testing the proposed RTD (2 mg/kg bw) and higher doses, 5 mg/kg bw and 2x 4 mg/kg bw (see *Clinical trials)*.

In order to support an anti-inflammatory indication, the applicant presented a randomized blinded GCP study involving a urate crystal synovitis model in dogs, where GALLIPRANT at an oral dose of 2 mg/kg SID was tested against a positive (robenacoxib) and a negative (placebo) group. A total of 12 dogs received each of the test items after overnight fasting in a 2 x 3 x 3 Latin-square design, with a minimum of 2 weeks between the start of each phase. Eleven dogs completed the study. The test items were administered once daily for three consecutive days prior to the injection of uric acid crystals in the knee joint, and once 2h post-injection. The endpoints (assessed over a time-period of 12h after uric acid stifle injection) were: Weight-bearing of the injected limb (assessed objectively by force plate analysis and subjectively); pain on palpation of the injected joint

(both assessed subjectively). Swelling (esp. joint swelling using a scale from 0 to 3) was the main endpoint that could be viewed as a purely subjective indicator of inflammation (without pain), and further supported by endpoints involving weight-bearing and pain-on-palpation scores. Treatment success was defined by the applicant as joint scores equal to 0 or 1.

In that study the difference between GALLIPRANT and placebo was statistically significant for certain endpoints and time points. The comparison of GALLIPRANT with robenacoxib through a non-inferiority analysis was inconclusive due to the small size of the study. The same comparison through a superiority analysis generally leads to an absence of demonstrated difference for the latest time-points (from 6h to 12h after the last administration), while for some endpoints, robenacoxib may be superior to GALLIPRANT at the earliest time points (before 6h after the last administration); this might suggest a slower onset of action for GALLIPRANT.

When specifically considering joint swelling, GALLIPRANT did not exert a significant preventative effect since at 0 and 3h post-treatment since there was no statistically significant difference seen, and at later time points (6, 9, 12 hours), significance was based on very few dogs with joint swelling scores >1. No biochemical, cytological or histopathological parameters were investigated; an anti-inflammatory effect was indicated only by the significant difference in the non-standardized joint swelling score frequencies with regard to placebo, which could partly relate to the alleviation of pain and the resulting increasing joint mobilization.

Overall, deficiencies in the study design and the statistical analysis were noted, and it is unknown as to which extent the results of this study would be relevant to the pathogenesis of dog osteoarthritis in a field situation. On the other hand, the differences between GALLIPRANT and placebo were statistically significant for the various endpoints and time points, which provided further support to the overall product efficacy in the treatment of pain.

Target animal tolerance

One pivotal GLP-compliant target animal safety study over nine months and two supportive published oral toxicity studies in dogs (10-days and 28 days) were provided to demonstrate the target animal safety of the product up to 28 days; in addition, safety data obtained from two clinical field studies were taken into account.

The pivotal TAS study was carried out with doses of 1, 6 and 50 mg grapiprant/kg bw given once daily for nine months by oral gavage to healthy Beagle dogs.

The study was not conducted in full compliance with VICH target animal safety guideline (EMEA/CVMP/VICH/393388, VICH Topic GL43) since the doses deviated from the recommended 1x, 3x and 5x recommended therapeutic dose (RTD) schedule and the final tablet formulation was not used (grapiprant was administered as a 0.5% methylcellulose suspension). Therefore, a pharmacokinetic bridging study was performed comparing the two formulations. Grapiprant given as the final tablet formulation resulted in higher systemic exposure compared to the suspension, where dose levels of 1, 6 and 50 mg/kg bw (oral suspension) would result in the same plasma levels as 0.75 mg/kg, 4.5 mg/kg and 30.5 mg/kg bw of the tablet formulation, i.e. approximately 0.5x, 2x and 15x RTD. Grapiprant was given by oral gavage in a fasted state (dogs were not offered food within two hours before treatment).

Oral administration (oral suspension) of 1, 6, or 50 mg/kg bw daily for 9 months was associated with mild gastrointestinal signs such as soft-formed faeces, faeces with mucous, and occasional blood seen in the faeces at all dose levels. The frequency of events was dose-dependent (163 events in controls, as compared to 328, 420 and 755 events in the low-, mid- and high-dose group, respectively). Mild regeneration of the mucosal epithelium of the ileum was observed in one male dog at 50 mg/kg bw.

Mild and transient changes in blood chemistry (e.g. decreases in mean serum albumin, decrease in mean total protein) were seen mainly in the high dose group, but were not associated with clinical signs. Furthermore, no treatment-related effects were found on liver or kidney function, or gross or histopathological findings of the liver, kidney, or stomach or in any coagulation parameters.

In other laboratory studies, severe adverse reactions in dogs were seen only at doses well above the recommended dose of 2 mg/kg bw. In healthy Beagle dogs, increased heart rate was seen at daily doses of 100 mg/kg bw and higher, whereas increased cardiac QTc intervals were observed at daily doses of 300 mg/kg bw. One fatality was observed at this dose level.

The most common adverse reactions seen in the clinical studies were gastrointestinal signs, i.e. vomiting, soft-formed or mucus faeces, diarrhoea and inappetence, all of which are included in the SPC. Vomiting was observed very commonly, whereas soft-formed faeces, diarrhoea and inappetence were commonly observed. Mild decreases in serum albumin and total protein were also reported.

Overall, CVMP concluded that the product is generally well-tolerated at the recommended dose, and can safely be used at the therapeutic doses for up to nine months. A safety margin of 2.25x the recommended dose has been established taking into account that at higher dose levels no serious adverse events were seen. The main reported adverse reactions of GALLIPRANT when used as recommended are mild and transient gastrointestinal signs. Mild decreases in serum albumin and total protein were also observed.

The safety of GALLIPRANT during pregnancy or lactation has not been demonstrated, and no data on reprotoxicity in dogs have been provided. Therefore, use in pregnant and lactating bitches as well as in breeding animals is contraindicated (see part 3).

During the first six months of clinical use of GALLIPRANT in the USA, some dogs accidentally consumed a high number of tablets. A statement has therefore been added to the SPC to store the product out of reach of animals to avoid any accidental ingestion.

Clinical field trials

Two clinical studies were conducted in the USA under field conditions to investigate the efficacy and clinical safety of GALLIPRANT in dogs for the proposed indications. One was a dose confirmation study, investigating different doses of GALLIPRANT (1 x 2 mg/kg bw (RTD), 1 x 5 mg/kg bw and 2 x 4 mg/kg bw), the second one was the pivotal field study .

Dose determination/confirmation study

A multicentre GCP-compliant placebo-controlled, randomised and blinded dose ranging field study was conducted using 331 privately owned dogs with naturally occurring osteoarthritis in at least one limb joint. The study was conducted in the USA and the dogs were of various breeds and ages (1 to 18 years). In addition to clinical signs, osteoarthritis was confirmed by radiography and veterinary assessment at the initial screening. Doses of 2 mg/kg bw once daily (SID), 5 mg/kg bw SID, or 4 mg/kg bw/day twice daily (BID), or placebo (BID) were administered for 28 days. The 2 mg/kg SID dose corresponded to the preliminary estimated dog AUC_{eff} , but for dogs in the fasted state (see above). In the present study however, in order to mimic practical field conditions of use, there was no standardisation of the feeding state therefore to account for the food effect that could occur a dose of 5 mg/kg bw SID was tested. A dose of 4 mg/kg bw BID was tested as well. A 4 mg/kg bw BID dose was used instead of a 5 mg/kg bw BID dose to ensure the highest dose any dog would get based on tablet dose band was under 10 mg/kg bw i.e., a 5X dose margin of safety based on the highest dose tested in the 9-month TAS study.

Efficacy assessment was based on a combination of owner assessments (Canine Brief Pain Inventory (CBPI) questionnaire) and veterinary assessments. The CBPI was completed once a week, where the owner graded their dog with regards to the Pain Severity Score (score 0-10), Pain Interference Score (score 0-10) and an overall impression on life quality (poor to excellent). The veterinary assessment was done at screening, on Day14 (±2), Day 28 (±3) and at any unscheduled withdrawal visit occurring prior to the Day 28 visit, and consisted of a Total Orthopaedic Score (TOS) with scores of 0 to 4 for each of the following parameters: Weight bearing on affected limb, lameness at walk, lameness at trot, willingness to raise contralateral limb, swelling of the joint under study, pain or resistance on palpation and forced movement of the joint under study, abnormal extension/range of motion of the joint under study.

The primary endpoint was the treatment success/treatment failure on day 28 compared to day 0, based on the dog owner's CBPI scale. For a dog to be considered a treatment success, the Pain Severity Score must be reduced by 1 or more, the Pain Interference Score must be reduced by 2 or more, and the overall impression must be the same or better than at Day 0. Secondary endpoints were the owners assessment of treatment success at Day 7, 14 and 21, and percent changes in the Pain Severity Score and Pain Interference Score from baseline (D0) to Day 7, 14, 21 and 28, and the veterinary assessment of changes in a the mean total orthopaedic score (TOS) from Day 0 to Day 14 and 28.

The treatment success rates at day 28 (primary endpoint) were 41.2% (35 out of 85 dogs) for placebo, 61.5% (56/91) for 2 mg/kg bw SID, 48.3% (43/89) for 4 mg/kg bw BID and 52.3% (45/86) for 5 mg/kg bw SID. The difference in success rates between the 2 mg/kg bw group and placebo group was statistically significant ($p = 0.0069$), but the difference between the two other treatment groups and placebo group was not significant. Also, the overall p-value for the dose effect generated from the generalized linear model was not statistically significant ($p = 0.0696$).

For secondary endpoints, the mean TOS values (10.1 – 10.9) were low considering the TOS range of 0 to 28, indicating a mild to moderate level of osteoarthritis among dogs at baseline. Compared to baseline, clinical signs improved in all four treatment groups at Day 14 and 28. All GALLIPRANT treated groups had a larger reduction compared to baseline than placebo, but the reduction was only statistically significant in the 2 mg/kg bw SID group and only at Day 14. When considering other efficacy endpoints and other time points, statistical significance was only obtained inconsistently, and again no increased efficacy with increased dose was clearly evident.

The applicant concluded that no added benefit appeared to be present from increasing the dose to 5 mg/kg bw SID or 4 mg/kg bw BID, considering the lower or similar level of efficacy and the higher frequency of adverse reactions at these doses. Therefore, the 2 mg/kg bw SID dose was chosen for evaluation in the pivotal field study. It was also concluded from this study that GALLIPRANT given twice daily (4 mg/kg bw BID) does not provide a benefit over once daily dosing (2 mg/kg SID).

Pivotal field study

The pivotal multicentre GCP-compliant field study was a placebo-controlled, randomised and blinded, and included 285 client-owned dogs with osteoarthritis in at least one limb joint. The study was conducted in the USA and the dogs included were representative for the target population, including various breeds, various ages (6 months to 16.8 years) and equally distributed between female and male dogs. The joints evaluated were typically the hip, elbow or stifle but other joints were also represented, including shoulder and tarsus. In addition to clinical signs, osteoarthritis was confirmed by radiography and veterinary assessment at the initial screening. GALLIPRANT given at a dose of 2 mg/kg bw (dose range of 1.5 to 2.9 mg/kg bw) once daily for 28 days was evaluated against placebo, using whole or half tablets. The efficacy endpoints were similar to those of the dose confirmation study,

i.e. primary endpoint was the treatment success based on the dog owner's CBPI scale at D28, and secondary endpoints included the owners' and the veterinarians' assessments .

For the primary endpoint and based on the Intention-to-Treat (ITT) population, treatment success rate at Day 28 in the GALLIPRANT group (45.4%) was higher than in the placebo group (32.6%), but the difference was not statistically significant (p = 0.08). (For the Per-Protocol-Population (PP) the corresponding success rate was 48.1% in the GALLIPRANT group and 31.3% in the placebo group (P=0.0315)). For the secondary endpoints, mean total orthopaedic scores (TOS) at baseline were approximately 10 in treatment and placebo groups, indicating a mild to moderate level of osteoarthritis at study start. At Day 14 and 28, clinical signs improved in both groups. However, a statistically significant difference in favour of GALLIPRANT compared to placebo was only noted at day 14 (p = 0.0064) and day 28 (p = 0.0242), in regards to differences in the Least Square (LS) means of the TOS.

Both clinical studies mostly involved dogs with moderate OA changes only, and the use of the product is therefore only recommended in dogs with mild to moderate forms of osteoarthritis. In both field studies, a rather high level of treatment failures according to the definition of the primary endpoint were observed at the proposed dose of 2 mg/kg, i.e. 54.6% in the pivotal field study and 38.5% in the dose confirmation study at day 28; even higher values were noted at earlier assessment time points. Based on the Day 28 results for the primary endpoint in the pivotal field trial, this means that the calculated number of dogs needed-to-treat (NNT) is approximately 8. This means that for every eight dogs treated, only one dog will benefit clinically (based on the primary endpoint) from GALLIPRANT treatment. In both studies, no restrictions were applied to the feeding state of the dogs. Since feeding is known to have a significant impact on the bioavailability of grapiprant in dogs, the applicant was asked to evaluate the impact of feeding on the efficacy of GALLIPRANT at the proposed dose. The CVMP also questioned the choice of primary/secondary endpoints, since veterinary assessments were considered of major importance.

To address these concerns of the CVMP, the applicant performed two combined analyses of the two field studies, one focused on the owner assessment success rate (CBPI) and one focused on the veterinarians' assessment (TOS). Generalized linear mixed models were used including treatment group as a fixed effect and study as a random term.

The results of the combined analysis, when comparing GALLIPRANT to placebo, show consistently statistically significant benefits of the 2 mg/kg SID administration to dogs regarding pain associated with osteoarthritis, at all time points, for both intention-to-treat and per-protocol populations. In the ITT population, for the primary endpoint (the owner assessment success rate at Day 28) the success rates were 51.3% (120/235) for GALLIPRANT and 35.5% (82/231) for the placebo group; this difference in favour of the product was statistically significant with a p-value of 0.0008.

The statistical re-analysis of the potential effect of the feeding state of dogs on the clinical response was inconclusive, i.e. no significant effect of the feeding state on the success rate could be demonstrated. This might be due to a relatively low power (e.g. the fed or fasted subgroups each represent a range of feeding conditions), or to confounding effects such as the severity of osteoarthritis, possibly associated to the feeding state. Since, there was a considerable decrease in bioavailability shown in a pharmacokinetic study in fed versus fasted dogs. To be in line with that finding and obtain an optimal pre-treatment fasting period, while remaining realistic in regard of practical constraints for the owners, It is recommended to administer this product on an empty stomach (e.g. in the morning), and at least one hour before the next meal.

The applicant discussed the clinical significance of the results of the clinical trials, by providing several literature studies in dogs or in human patients suffering from osteoarthritis and treated with NSAIDs. Although the limitations of this approach are recognized, mainly in that studies with very variable

designs, methods and target populations are compared, overall it is shown that the NNT and size effect (Cohen's d) values obtained with GALLIPRANT are in the same range as those reported for other NSAIDs in the submitted osteoarthritis studies.

Anti-inflammatory claim:
The two clinical trials focussed primarily on treatment success in terms of pain relief and improvement of clinical signs, but not the anti-inflammatory effect. The applicant considered that a reduction in pain was a consequence of a reduction of inflammation, but this was not accepted as an adequate justification for this selective EP_4 receptor antagonist. Since the EP_4 receptor results in the production of only part of the inflammatory cascade and is present on specific neurons (e.g. DGR neurons), the premise of linking pain and inflammation was questioned. In order to further address the concerns raised for an anti-inflammatory indication, the applicant presented a randomized blinded GCP study involving a urate crystal synovitis model in dogs, where GALLIPRANT at an oral dose of 2 mg/kg SID was tested against a positive (robenacoxib) and a negative (placebo) group for study design, see dose confirmation). Overall, deficiencies in the study design and the statistical analysis were noted, and it is unknown as to which extent the results of this study would be relevant to the pathogenesis of dog osteoarthritis in a field situation.

Therefore, the CVMP concluded that a clinically relevant anti-inflammatory effect for osteoarthritis was not considered sufficiently proven.

Conclusions:
Results from the two clinical field trials showed a higher rate of treatment success in terms of pain relief and improvement of clinical signs in dogs with mild to moderate stages of osteoarthritis treated with GALLIPRANT at the proposed single daily dose of 2 mg/kg bw over 28 days compared to dogs treated with placebo. However, a clinically proven anti-inflammatory effect for osteoarthritis was not considered sufficiently demonstrated.

The combined analyses of the two field studies provided the basis for a positive opinion for GALLIPRANT as a treatment of pain associated with osteoarthritis in dogs. For example, the combined analysis demonstrates consistent positive benefits of the single daily 2 mg/kg administration to dogs with osteoarthritis, when comparing GALLIPRANT to placebo, for important time points and endpoints, for both owner and veterinary assessments. These differences are all statistically significant for both full analysis and per-protocol sets. However, the use of GALLIPRANT is only recommended in dogs with mild to moderate osteoarthritis. Moreover, if no clinical improvement is apparent after 14 days, treatment with GALLIPRANT should be discontinued and different treatment options should be explored in consultation with the veterinarian.

Finally, the product should only be administered to dogs with an empty stomach (e.g. in the morning), and at least one hour before the next meal.

Overall conclusion on efficacy

Pharmacodynamics
Overall, the pharmacodynamic and pharmacokinetic characteristics of grapiprant are satisfactorily documented and evaluated in dogs. Grapiprant is a new analgesic and anti-inflammatory drug, acting selectively as antagonist of the EP_4 receptor, which is the primary mediator of prostaglandin E_2 (PGE_2), a clinical mediator of pain and inflammation. A series of *in vitro* and *in vivo* studies in various rodent pain and inflammation models showed that grapiprant was able to block PGE_2-elicited pain and inflammation by blocking the EP_4 receptor.

In an experimental study in dogs, using acute inflammation induced by uric acid, an acute anti-inflammatory effect was indicated by a significant reduction in joint swelling score frequencies

compared to an untreated control group. However, the study design showed some deficiencies and also, it is not known to which extent the reduction of acute inflammation in this model could be extrapolated to the pathogenesis of dog osteoarthritis in a field situation.

Pharmacokinetics
Grapiprant is rapidly absorbed from the gastrointestinal tract. The rate of absorption is affected (i.e. delayed) by feeding, oral bioavailability is approximately 90% (fasted dogs). Grapiprant is highly protein bound (95%). The main route of excretion is biliary and total faecal excretion accounts for 65% of the dose. The elimination half-life of grapiprant is approximately 4.6 to 5.7 hours.

Tolerance
GALLIPRANT was generally well-tolerated at the recommended dose for up to 28 days. The most common adverse reactions seen were gastrointestinal signs (e.g. vomiting, soft-formed or mucous faeces, diarrhoea and inappetence), which are included in the SPC. Mild decreases in serum albumin and total protein were also reported. In healthy Beagle dogs, increased heart rate was seen at daily doses of 100 mg/kg bw and higher, whereas increased cardiac QTc intervals were observed at daily doses of 300 mg/kg bw. One fatality was also observed at this dose level. It was concluded that severe clinical symptoms in healthy young dogs occur at dose rates well above the recommended dose and that the safety margin of 2.25x the recommended dose is acceptable.

Dose justification
Dose justification was based on dose extrapolation from rat and human effective doses. Although the dose justification was not fully supported by CVMP, it was confirmed by the clinical studies.

Dose determination:
Four non-GLP exploratory efficacy studies in canine experimental models of osteoarthritis were conducted, investigating doses of 1 mg/kg, 2 mg/kg, 3 mg/kg, 10 mg/kg and 30 mg/kg bw against a positive control (firocoxib) and/or a negative control. However, due to deficiencies in the disease model, study design and insufficient numbers of animals, the studies are considered as proof-of-concept only.

Clinical studies

Dose confirmation / field study
Results from two clinical field trials (one dose determination and one pivotal field trial) showed a higher rate of treatment success in terms of pain relief and improvement of clinical signs in dogs with osteoarthritis treated with GALLIPRANT at the proposed single daily dose of 2 mg/kg bw over 28 days compared to dogs treated with placebo. Although these improvements were inconsistent and no clear trends in efficacy were demonstrated, a later combined analysis of the two field studies demonstrated consistent positive benefits of GALLIPRANT when administered orally at single daily dose of 2 mg/kg bodyweight (SID) to dogs regarding pain associated with mild-to moderate cases of osteoarthritis, when comparing GALLIPRANT to placebo, for important time points and endpoints, based on both owners' and veterinarians' assessments.

However, a clinically proven anti-inflammatory effect in dogs with osteoarthritis was not considered sufficiently demonstrated.

Individual variations in response to treatment are mitigated for by SPC recommendations, for example by administration of the product to dogs with an empty stomach, as well as re-assessment if no response after 14 days.

Part 5 – Benefit-risk assessment

Introduction

GALLIPRANT tablets for dogs contain grapiprant as active substance, a non-steroidal prostaglandin EP_4 receptor antagonist, resulting in selective reduction of PGE_2-elicited pain and inflammation. The product is intended for use in dogs for the treatment of pain and inflammation associated with osteoarthritis, at a daily dose of 2 mg per kg bodyweight for up to nine months.
The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application).

Benefit assessment

Direct therapeutic benefit

On the basis of two placebo-controlled field studies, it was concluded that administration of GALLIPRANT at the recommended dose of 2 mg/kg bw once daily for a period of 28 days resulted in improvements in owner assessment scores of pain severity, pain interference and life quality in dogs with mild to moderate osteoarthritis.

The results were confirmed by a veterinary assessment using a composite orthopaedic score. A combined analysis of the two field studies demonstrated consistent positive benefits of the 2 mg/kg SID administration to dogs regarding pain associated with mild to moderate osteoarthritis, when comparing GALLIPRANT to placebo, for important time points and endpoints, for both owner and veterinary assessments.

However, a clinically relevant anti-inflammatory effect in dogs with osteoarthritis was not sufficiently demonstrated.

Additional benefits

None identified.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

Safety

Risks for the target animal:

GALLIPRANT is generally well tolerated in dogs at the therapeutic doses of 2 mg/kg bw. The main reported adverse reactions of GALLIPRANT when used as recommended were mild and transient gastrointestinal signs. Mild decreases in serum albumin and total protein were also observed. In the absence of data, use in pregnant and lactating bitches as well as in breeding animals is contraindicated.

Risk for the user:

The most severe risk is accidental ingestion by a child. An appropriate warning is included in the SPC and the product is intended to be marketed in child-resistant packages. Despite the absence of any

developmental and reproductive toxicological data, exposure of pregnant women or women of child-bearing age is expected to be low, therefore a SPC warning for this type of user was not considered necessary.

Risk for the environment:

GALLIPRANT is not expected to pose a risk for the environment when used according to the SPC.

Risk management or mitigation measures

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

User safety risks have been identified, mainly the risks associated with exposure in children. These risks are mitigated by the presentation of the product in child-resistant packaging.

Evaluation of the benefit-risk balance

Based on the data presented, the overall benefit-risk is considered positive.

The applicant applied for the following indication: For the treatment of pain and inflammation associated with osteoarthritis in dogs. The product has been shown to be efficacious for pain associated with veterinary assessed mild to moderate osteoarthritis, and the CVMP agreed to the following indication(s): ”For the treatment of pain associated with mild to moderate osteoarthritis in dogs.”

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users, the environment and consumers, when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

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 GALLIPRANT is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

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