15 February 2018
EMA/101046/2018
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Clevor (EMEA/V/C/004417/0000)

International non-proprietary name: ropinirole

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

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Introduction

The applicant Orion Corporation submitted on 27 September 2016 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Clevor eye drops, solution in single-dose containers for dogs, 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 17 March 2016 as Clevor contains a new active substance (ropinirole) which is not yet authorised as a veterinary medicinal product (VMP) in the Union.

The applicant applied for the following indication: "Induction of vomiting in dogs."

The active substance of Clevor is ropinirole, a dopamine agonist which is rapidly absorbed into the systemic circulation after administration as a solution onto the eye surface, and then induces emesis. The target species are dogs. The route of administration is ocular use.

Clevor eye drops, solution in single-dose container, contains 30 mg/ml ropinirole and is presented in blow-fill-seal (BFS) plastic containers with a nominal content of 0.6 ml. The outer packs contain 1, 2, 4, 5, 6, 8 or 10 containers.

The rapporteur appointed is Cristina Muñoz Madero and the co-rapporteur is Eva Lander Persson.

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

On 15 February 2018, the CVMP adopted an opinion and CVMP assessment report.

On 13 April 2018, the European Commission adopted a Commission Decision granting the marketing authorisation for Clevor.

Scientific advice

Not applicable.

MUMS/limited market status

The applicant requested classification of this application as MUMS/limited market by the CVMP, and the Committee confirmed in May 2015 that, where appropriate, the data requirements in the relevant CVMP guideline(s) on minor use minor species (MUMS) data requirements would be applied when assessing the application. MUMS/limited market status was granted as the indication in dogs is considered a minor use.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated 14.01.2015) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third

country.

Manufacturing authorisations and inspection status

Manufacture, processing and control of the dosage form takes place within the EEA GMP certifications, which confirm the date of the last inspections and show that the sites are authorised for the manufacture of this veterinary dosage form, have been provided.

Batch release takes place at Orion Corporation, Orionintie 1, Espoo, Finland which holds a manufacturing authorisation issued on 12 August 2015 by Finnish Medicines Agency (Fimea), Finland. GMP compliance was confirmed by the competent national authority Finnish Medicines Agency (Fimea), Finland.

Manufacture of the active substance takes place outside the EEA. GMP declarations for the active substance manufacturing sites were provided from the Qualified Person (QP) at the EU batch release site. The declarations were based on on-site audits by the manufacturing site responsible for batch release.

Additionally, quality control testing of the active substance in accordance with the Ph. Eur. current monograph for ropinirole hydrochloride when entering in the EU takes place within the EEA. GMP compliance was confirmed by the competent national authority.

Overall conclusions on administrative particulars

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

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

Part 2 - Quality

Composition

The product Clevor is a very slightly yellow to yellow, sterile, aqueous, eye drop solution in single-dose containers containing 30 mg/ml of ropinirole (equivalent to 34.2 mg ropinirole hydrochloride) as the active substance.

Other ingredients are citric acid monohydrate, sodium citrate, sodium chloride, hydrochloric acid and sodium hydroxide and water for injections.

The lack of a preservative is justified because it is intended for single use, even though a second dose could be administered after 15–20 minutes of the first administration, if needed.

The composition of the product is appropriately stated.

Containers

The primary packaging is a 1 ml translucent low density polyethylene (LDPE) plastic blow-fill-seal (BFS) single-dose container, with a nominal content of 0.6 ml from which the eye drops are

administered by squeezing. Each container is sealed in an individual sealed aluminium foil laminate pouch. The sealed pouches are further packed in outer cardboard cartons, together with a package leaflet. The proposed pack sizes are a single pack of 1 single-dose container and multipacks of 2, 4, 5, 6, 8 and 10 single-dose containers. The pack sizes are consistent with the dosage regimen and duration of use.

The material of construction of the primary containers (LDPE) complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The choice of the container-closure system has been validated by stability data and is adequate for the intended use of the product.

Development pharmaceutics

The aim of the development pharmaceutics was to formulate an ophthalmic medicinal product with ropinirole as the active substance which had an osmolality and pH close to that of dogs' tear film, would be easy to be administered, was physically and chemically stable, and ideally had a shelf life of 3 years. The selection of this active substance, route of administration and dosage form has been justified.

All excipients are well known pharmaceutical ingredients, commonly used in ophthalmic dosage forms and their quality is compliant with Ph. Eur. standards, except for the pH adjusting solutions, although the raw materials used to manufacture them do meet the respective Ph. Eur. requirements.

There are no novel excipients used in the finished product formulation.

The list of excipients is included in section 6.1 of the SPC.

The selection of the container-closure system is described. 1 ml LDPE translucent single-dose containers were chosen. The single-dose containers are sealed in an aluminium foil laminated pouch to protect the medicinal product from light.

The final formulation intended for marketing was the simplest formulation possible based on the results from the stability study, local tolerance study (eye irritation) and clinical study; only small changes were made in the formulation for manufacturing reasons. The final formulation and selected container were used in the clinical field study.

Regarding the manufacturing process, critical quality attributes were identified, as well as the actions taken to improve them and the control strategy.

The development pharmaceutics of the formulation has been explained in a comprehensive and detailed manner.

Method of manufacture

The manufacturing process comprises the preparation of the bulk solution, a preliminary filtration to achieve a low bioburden bulk solution, followed by the sterilisation by filtration through two sterilizing grade cartridge filters and then the aseptic BFS process starts with the formation of the plastic single-dose containers from the polymer resin, their filling and sealing in a continuous operation. Finally, the single-dose containers are individually sealed into aluminium foil laminate pouches, and the pouches are further packaged into cardboard cartons (with a leaflet).

The BFS process is considered a standard manufacturing process for the proposed manufacturer.

The maximum holding times have been verified using data from a technical commercial scale batch and during media fills validation.

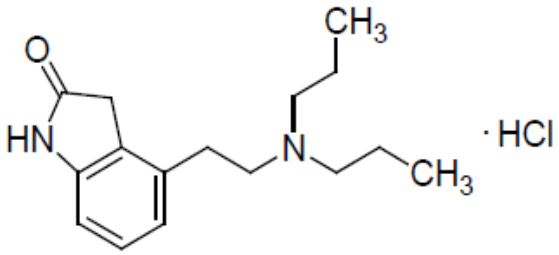
The manufacturing process and in-process controls have been described in adequate detail. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

With regard to the validation of the manufacturing process, some validation data has been provided from pilot scale batches to demonstrate that the manufacturing process is capable of producing the finished product of intended quality and in a reproducible manner. No production scale validation data have been presented. However, because this veterinary medicinal product has been classified as a MUMS product, the provision of the process validation scheme, together with an undertaking that three consecutive production scale batches will be fully validated before commercial launch of the product, is considered sufficient as pre-authorisation data and is in accordance with the CVMP Guideline on quality data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market (EMA/CVMP/QWP/128710/2004-Rev.1).

Control of starting materials

Active substance

The chemical name of ropinirole hydrochloride is 4-[2-(Dipropylamino)-ethyl]-1,3-dihydro-2*H*-indol-2-one hydrochloride and it has the following structure:



Ropinirole hydrochloride is a powder, freely soluble in water.

Ropinirole has a non-chiral molecular structure.

Polymorphism has been observed for ropinirole. According to several patents, three polymorphic forms have been identified, and the active substance used in this medicinal product is polymorph Form I.

There are two manufacturers of the active substance and the information on the active substance is provided according to the Active Substance Master File (ASMF) procedure for both of them.

A monograph for ropinirole hydrochloride was implemented in the supplement 8.7, April 2016 of the European Pharmacopoeia. All the tests and limits in the specification proposed by the finished product manufacturer comply with those of the Ph. Eur. monograph. The following additional parameters have however been added: palladium content, residual solvents and microbiological control. Further information, including validation data, have been provided regarding the analytical method used in the reanalysis of residual solvents performed by the finished product manufacturer at the reception of the batches of active substance. Batch data from testing performed by the finished product manufacturer have been provided, as well as the qualification against the Ph. Eur. standards of the working reference standard(s) used by the finished product manufacturer.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on the chemistry of new active substances. Potential and actual impurities were well discussed with

regards to their origin and characterised. Ropinirole is synthesised in 2 or 3 main steps (depending on the manufacturer) with a final purification step. Commercially available and well defined starting materials with acceptable specifications are used. Appropriate information has been provided of the synthetic steps prior to the defined starting materials, the suppliers, residual solvents and impurities. Adequate in-process controls are applied during the syntheses. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacture of the active substance has been provided in the restricted parts of each of the two ASMFs.

The specifications of the active substance proposed by both suppliers are considered appropriate. Compliance with the recently implemented Ph. Eur. monograph for ropinirole hydrochloride is confirmed.

The analytical methods have been adequately described and non-compendial methods appropriately validated in accordance with VICH guidelines GL1 & 2 on the Validation of analytical procedures.

Batch analysis data from manufacturers of the active substance have been provided. The results are within the specifications and are consistent from batch to batch. Additional batch analyses data have been provided of the analysis performed by the finished product manufacturer in accordance with the final specifications.

Similar container-closures are proposed for storing the active substance for both ASMFs (low density polyethylene bags, tied and placed in a drum).

Stability data on nine batches of active substance from the proposed first manufacturer are provided: a preliminary study with three pilot batches, a study with three production batches and an on-going study with three production batches. They are stored in the intended commercial package for 60 months (for the on-going study data available is up to 36 months) under long term conditions at 25 ºC/60% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH, according to the relevant VICH guidelines.

Stability data on six production batches of active substance from the proposed second manufacturer are provided: an initial study with three batches and an on-going study with three batches. They are stored in the intended commercial package for 60 months (for the on-going study data available is up to 24 months) under long term conditions at 25 ºC/60% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH, according to the relevant VICH guidelines.

Photostability testing in accordance with VICH guideline GL5 (Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances) was performed on one batch of the active substance from each manufacturer. Results from stress conditions (acid conditions, basic conditions, oxidation conditions, high temperature and UV radiation) were also provided on one batch from each manufacturer.

All tested parameters were within specification. No significant change was observed in any parameter tested, showing that the active substance is stable when stored in the proposed containers.

The stability results justify the proposed retest period of 3 or 5 years in the proposed container without any special storage conditions for the active substance depending on the manufacturer.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with their

respective current Ph. Eur. monographs except for the pH adjusting solutions, although the ingredients used in their manufacture meet the Ph. Eur. requirements. Representative certificates of analysis are included in the dossier.

The information provided on the excipients is acceptable.

Regarding the nitrogen used during manufacture of the medicinal product, compliance with the relevant Ph. Eur. monograph is confirmed, as well as confirmation that it is sterilized by filtration (during the manufacturing process).

There are no novel excipients used in the finished product formulation.

The list of excipients is included in section 6.1 of the SPC.

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.

A valid TSE declaration in compliance with the current Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01-Rev.3) is provided.

Control tests on the finished product

The finished product release specification includes appropriate tests for this kind of dosage form and comprises: appearance of the dosage form, appearance of the single-dose container, identification (HPLC/UV), pH (Ph. Eur.), uniformity of dosage units (mass variation) (Ph. Eur.), assay by HPLC, impurities by HPLC and sterility (Ph. Eur.). The specifications proposed for use at release and during shelf life are acceptable.

The control methods are described and appropriately validated in accordance with the VICH guidelines.

Batch analysis results are provided for four pilot batches and one production batch confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Stability studies were performed under VICH conditions and comprise the primary stability study, an in-use stability study, photostability study and a freeze-thaw stability study.

Stability data from three pilot scale batches (which were more than 10% of the proposed commercial scale) of the finished product stored under long-term conditions for up to 18 months at 25 ºC/60% RH and for 6 months under accelerated conditions at 40 ºC/75% RH, according to VICH guideline GL3 (Stability testing of new veterinary drug substances and medicinal products), were provided. The batches of the finished product were identical to those proposed for marketing and were packed in the primary and secondary packaging proposed for marketing.

Samples were tested for appearance of the dosage form, appearance of the single-dose container, assay of ropinirole HCl, impurities, pH, and sterility. Osmolality was tested at 6 months in the accelerated storage conditions and at 24 months in the long-term storage conditions.

In addition, one pilot scale batch was exposed to light as defined in VICH guideline GL5 (Stability testing: photostability testing of new veterinary drug substances and medicinal products). The results showed that although the solution is sensitive to light, the medicinal product is stable when the primary package (BFS container) is stored in the secondary packaging (aluminium foil laminate pouch).

The freeze-thaw stability study was performed. The solution was proven to be stable in this study.

The analytical procedures used are stability indicating and have been appropriately validated.

No significant changes were observed in the studies conducted confirming that the product is stable when the primary container is kept in the secondary packaging under the conditions tested.

A shelf life of 30 months without any special temperature storage conditions, when the product is kept in the secondary pouch, is acceptable at present.

Although information is not submitted to demonstrate that the medicinal product can withstand low relative humidity conditions, the absence is acceptable based on the water loss data provided in the development pharmaceutics and the intention to always keep the container in the pouch, even after opening. In-use stability studies have been conducted on one pilot scale batch. The results showed that the solution is very stable because no significant changes were observed in any of the tested parameters. The proposed in-use shelf life of 30 minutes is deemed acceptable and in line with the intended use. Some additional precautions have been proposed in the SPC (and other product information) regarding in-use storage.

Finally, the following commitments are provided in the dossier:

1. A full process validation of the manufacturing and filling process will be performed prior to commercial launch with three consecutive batches of commercial batch size.
2. The on-going primary stability study will be continued with all the three batches stored at 25 °C/60% RH for up to 36 months.
3. A VICH stability study on the first three commercial production scale batches of the product will be performed.
4. An in-use stability study will also be carried out on one batch of the product at the end of its shelf life.

Overall conclusions on quality

The product Clevor is an aqueous eye drops solution presented in single-dose blow-fill-seal LDPE containers containing 0.6 ml.

Pharmaceutical development of this new product focused on the formulation of a stable unpreserved eye drop solution with an appropriate pH and osmolality for use in dogs, and adequate stability. The development pharmaceutics has been explained in comprehensive and detailed manner.

The manufacturing process of the solution is simple and consists of dissolution of the active substance and the excipients followed by the sterilisation by filtration and aseptic filling into the single-dose blow-fill-seal LDPE containers.

As the manufacturing method is a standard process for the stated manufacturing site and validation data on pilot-scale batches were provided, it was accepted that full scale validation would be performed post-authorisation on the first 3 commercial scale batches, in accordance with the CVMP Guideline on the quality data requirements for veterinary medicinal products intended for minor use or

minor species (EMEA/CVMP/QWP/128710/2004). The applicant has provided both a protocol for the process validation study and a commitment to submit the data post-authorisation.

Documentation is provided for the ropinirole hydrochloride from two different active substance manufacturers. In both cases the ASMF procedure is used. The information provided in both ASMFs is considered appropriate, as well as the reanalysis performed by the finished product manufacturer at the reception of the batches of active substance.

All excipients are well known ingredients and their quality is appropriately controlled.

The finished product specifications proposed for use at release and at the end of shelf-life include parameters appropriate for the dosage form. Satisfactory batch data for three full scale batches manufactured at the proposed site are provided.

The product is very stable with little inter-batch variation observed in stability studies. The stability data presented is considered adequate to support a shelf life of 30 months without any special temperature storage conditions, when the product is kept in the secondary packaging (pouch).

In general, comprehensive and clear quality information has been provided in the dossier to support the authorisation of this medicinal product, and current regulations and guidelines have been taken into account.

In addition, the applicant is recommended to provide the following information post-authorisation:

- The leachables studies will be continued to cover the shelf-life period
- Process validation studies should be performed on the first 3 commercial batches.
- The table of specifications included in section 3.2.P.5.1 should be codified
- The first 3 batches produced for commercial release should be placed in a stability study for which the protocol has already been approved.
- The on-going primary stability study will be continued with all the three batches stored at 25 °C/60% RH for up to 36 months.
- An in-use stability study will also be carried out at the end of its shelf life.

Part 3 – Safety

The active substance ropinirole hydrochloride, a full dopamine agonist with high selectivity for the dopamine D_2-like receptor family (D_2, D_3 and D_4 receptors), is a new active substance not authorised for use in a veterinary medicinal product in the EU before. A full safety file in accordance with Article 12(3)(j) has been provided combining some bibliographic data and some new studies performed with the intended formulation.

The pharmacological and toxicological properties of ropinirole have been characterised and described in the dossier based on available literature and laboratory studies performed by the applicant.

Pharmacodynamics

Ropinirole has been shown to induce emesis in dogs by binding to both central and peripheral dopamine receptors. Some secondary effects have been described on the cardiovascular system, which are considered to be of limited relevance due to the expected sporadic use of the product.

For more detailed information on the pharmacodynamic properties of ropinirole, please see part 4 and section of studies of other effects of this report.

Pharmacokinetics

Ropinirole is rapidly absorbed after oral administration. In a tablet formulation its bioavailability is about 50% in humans. However, it is nearly completely absorbed in aqueous solution. Ropinirole may be absorbed through intact skin; however, systemic exposure in dogs via the subconjunctival mucosa is limited, following rapid absorption a rather low systemic bioavailability of 23% was shown. Parent ropinirole and its metabolites are widely distributed in tissues and are readily able to cross the blood-brain barrier. Ropinirole is extensively metabolized; although the predominant pathway of metabolism is species-dependent. Ropinirole is excreted rapidly, mainly as metabolites and predominantly in the urine of all animal species and man.

For more detailed information on the pharmacokinetic properties of ropinirole, please see part 4 of the report.

Toxicological studies

Published literature references have been provided to describe the single and repeated dose toxicity, the reproductive toxicity and the carcinogenicity of ropinirole.

Regarding the genotoxicity, two pivotal studies have been conducted following OECD guidance (bacterial mutation test and in vitro test for chromosomal effects in mammalian cells). The in vivo chromosomal effects have been documented through published literature.

In addition, eye irritation was studied in the PK studies conducted by the applicant, and a skin sensitization test following OECD guidance has also been provided.

Single dose toxicity

The results obtained from the published literature show that ropinirole possesses low acute toxicity, with LD_{50} values in rats of 396 mg/kg bw (males) and 581 mg/kg bw (females) after oral administration, and 71 mg/kg bw (males) and 85 mg/kg bw (females) after intravenous administration. In monkeys, an approximate lethal dose was derived after oral administration (702 mg/kg bw). The main toxicological signs appear to be related with the pharmacological effect of ropinirole hydrochloride.

Two mammalian species and two different routes of administration have been reported in the submitted references. The methods used and the observations made throughout the study are comparable to those of the OECD guideline and the results are therefore considered reliable. As no safe toxicological reference values were obtained the study is not useful for quantitative characterisation of risks in the user risk assessment.

Repeat dose toxicity

Throughout the published literature on repeated dose toxicity in rats and Cynomolgus monkeys, no major toxic effects were observed, except for centrally and peripherally mediated clinical signs related to the pharmacological effect of ropinirole. The inhibitory effect of ropinirole as a dopamine agonist on

prolactin secretion was shown in these studies in both species, producing increased incidence of Leydig cell hyperplasia of the testis in the males and the presence of oestrogen dominance in drug-treated females in rats. However, the presence of prolactin responsive receptors (luteinising hormone-releasing hormone [LHRH] receptors) in Leydig cells appear to be unique to rats and therefore the risk for hyperplastic changes in testes in other species is considered negligible (Alison R et al., 1994). Due to the increased number of corpora lutea in rats at ≥10 mg/kg bw/day after one month and at ≥50 mg/kg bw/day after one year (5, 50 and 100 mg/kg bw/day), the NOAEL was derived by the applicant at the next lower dose level (5 mg/kg bw/day). Based on the clinical signs (including convulsions in one animal) and foci of hepatocellular alterations (no enzyme induction of e.g. CYP P450 was associated with these findings to suggest an adaptive change to enzyme induction) observed at all dose levels, the NOAEL in the 1-year study is considered to be <5 mg/kg bw/day. For monkeys, the NOAEL was derived at the mid dose level (5 mg/kg bw/day) based on effects at the high dose (15 mg/kg bw/day), centrally or peripherally mediated clinical signs in the 1-month study and changes in organ weights at the high dose in the 1-year study, respectively.

The potential adverse effects of ropinirole after repeated oral administration has been investigated in two mammalian species (other than the intended target species) for 1 month and 1 year periods. Comprehensive observations were made in the studies and the results are considered reliable and representative of physiological and/or pathological changes induced by repeated administration of the active substance. Toxicological reference values (NOAELs) were obtained for rats and monkeys after oral administration of ropinirole, of which the values from the 1-month studies are considered the most relevant for the assessment of target animal safety and user safety. The lack of a NOAEL in the 1-year study in rats is therefore not considered critical for the safety evaluation of the product.

Tolerance in the target species of animal

The tolerance in the target animal is described under Part 4.

Reproductive toxicity

Reproductive and developmental toxicity has been documented through bibliographical studies on three different species (rats, rabbits and mice).

No reproductive toxicity of ropinirole was observed in either male or female rats up to the highest dose tested (125 mg/kg bw/day over 107 days in males and 100 mg/kg bw/day in females treated from 14 days prior to the Day of mating and from Days 9–20 post-coitus and treatment at lower doses (5 mg/kg bw/day) between and after these periods (20 mg/kg bw/day until day 21 post-partum).

Developmental toxicity was observed in rats when females were treated on Days 8–15 post-coitus at ≥ 120 mg/kg bw/day (increased post-implantation loss, foetal death and decrease in mean foetal weight at doses ≥120 mg/kg bw/day and skeletal variations and digital malformations at 150 mg/kg/day) which also showed maternal toxicity expressed by convulsions and a transient decrease in bodyweight and food and water consumption. The NOAEL for developmental effects in rats is 90 mg/kg bw/day. In rabbits, no developmental toxicity was observed after treatment at doses of up to 20 mg/kg bw/day on Days 6–18 of gestation. This dose, however, had resulted in reduced maternal bodyweight and clinical signs attributable to the pharmacology of ropinirole. The NOAEL for developmental effects in rats is 20 mg/kg.

In the exploratory study in male mice, high ropinirole doses of 50, 75 and 100 mg/kg bw/day were tested. After administration over 21 days, the authors reported significant dose-dependent increases

in the frequencies of sperm abnormality and chromosomal aberrations in germ cells compared to controls.

In addition, in the repeated dose toxicity studies, the inhibitory effect of ropinirole as a dopamine agonist on prolactin secretion was shown, producing increased incidence of Leydig cell hyperplasia of the testis in the males and the presence of oestrogen dominance in drug-treated females. However, the presence of prolactin responsive receptors (luteinising hormone-releasing hormone [LHRH] receptors) in Leydig cells appear to be unique to rats and therefore the risk for hyperplastic changes in testes in other species is considered negligible.

Genotoxicity

The genetic toxicology potential of ropinirole was evaluated in a standard test battery in accordance with VICH guideline GL23. However, the in vivo chromosomal effects have been documented through published literature. Additional literature reports relating to the genotoxicity of ropinirole were also available (Kirkland et al (2016) and Brambilla and Martelli (2009)).

In the Ames test performed by the applicant according to OECD GL 471, ropinirole was negative for induction of reverse mutations in the five tester strains of Salmonella typhimurium in the presence and absence of metabolic activation.

In the in vitro Human Lymphocyte Chromosome Aberration Assay performed by the applicant according to OECD GL473, ropinirole did not induce biologically relevant increases in the frequency of structural chromosome aberrations, although statistically significant increases were observed at the highest tested dose for the 20 hour treatment.

The reference provided to document the in vivo chromosomal effects of ropinirole is not consistent with the current OECD guidelines (OECD GL 474 and 475). Some relevant general test conditions are not described on the literature such as the type of oral administration of the product. Only male animals are used in the study and no positive control animals are included. The treatment schedule and dose levels do not follow OECD guidelines recommendations. The number of cells per animal analysed for the bone marrow chromosome aberration test is not sufficient according to OECD GL 475. Some of the study endpoints do not strictly comply with the OECD standards. Lack of information on any toxic effects on the bone marrow, and lack of systemic exposure data are considered critical for the assessment of the relevance of the results. Due to the deficiencies, the validity of the positive observed effects, at the chromosome level, is questionable. It was concluded that the total weight of evidence, including the overall negative in vitro assays provided in this application (Ames test and a chromosomal aberration test in human peripheral blood lymphocytes) and in published literature reports together with the absence of relevant findings in carcinogenicity studies are sufficient to conclude that ropinirole does not have genotoxic potential. This conclusion is further supported by negative studies reported in relation to the FDA's approval of ropinirole for human use (in vitro; Ames test, an HPRT gene mutation in mouse lymphoma cells, a chromosomal aberration test in human peripheral blood lymphocytes, in vivo; a mouse bone marrow micronucleus test, and most importantly, negative carcinogenic studies in rodents [only species-specific findings of neoplastic changes were indicated]).

Carcinogenicity

No carcinogenicity study was conducted for this application. The data from publicly available carcinogenicity studies indicate that ropinirole induces neoplastic lesions in rodents by a

species-specific mechanism.

In the rat, the only drug-related neoplastic lesions were Leydig cell hyperplasia/adenomas most obviously resulting from the hypoprolactinaemic effect induced by ropinirole. This mechanism is typical also for other dopamine agonists and the lesions are considered to be a species specific phenomenon having no relevance to non-rodent species.

In mice, the only lesion was an increased incidence of benign uterine endometrial stromal polyps in high dose females. Uterine stromal polyps in rodents are a common non-cancerous finding and the relevance to other species is questionable.

In domestic dogs, endometrial stromal polyps are fairly uncommon and the lesions do not show evidence of preneoplasia.

It can be concluded that Clevor to be used sporadically does not pose any carcinogenicity risk to either the target animal species or to the users of the product.

Studies of other effects

Eye irritation: Eye irritation in dogs was studied on ropinirole solutions and the final product as part of the pharmacological and target animal safety studies. Ropinirole, at concentrations of 10–50 mg/ml, caused mild to moderate symptoms of eye irritation in dogs which improved two hours after exposure and completely resolved within 24 hours post-dose. Although no formal eye irritation test was conducted following OECD guidance, the product can be classified as a moderate eye irritant based on the target animal safety studies.

Skin sensitisation: A GLP-compliant study local lymph node assay was conducted according to OECD GL 429 to evaluate if ropinirole induces skin sensitisation. No irritation of the skin or sensitisation potential was observed for ropinirole hydrochloride concentrations of up to 50%.

Cardiovascular effects: Cardiovascular effects of ropinirole were studied in dogs as part of preliminary assessments in drug development, and as part of the efficacy studies. Increased heart rate and slight increasing effects on diastolic blood pressure has been described. In addition, data from public literature revealed that ropinirole blocked hERG channels in vitro, and caused moderate hypotension, tachycardia, and QTc extension at its maximally tolerated acute intravenous dose of 20 mg/kg in dogs.

Endocrine dysfunction: The inhibitory effect of ropinirole as a dopamine agonist on prolactin secretion has been described in rats, producing increased incidence of Leydig cell hyperplasia of the testis in males, and the presence of oestrogen dominance in females. However, the presence of prolactin responsive receptors (luteinising hormone-releasing hormone [LHRH] receptors) in Leydig cells appear to be unique to rats, and therefore the risk for hyperplastic changes in testes in other species is considered negligible.

Use in humans: The use of ropinirole in humans is widely documented. Ropinirole is authorised for treatment of Parkinson's disease and restless legs syndrome. Total oral daily doses of ropinirole given as immediate release tablets to adults range from 0.75 mg to 24 mg/person. A comprehensive summary of clinical trials, treatment follow-up studies and case reports has been provided. Taken together, the most common adverse side effects observed at effective treatment concentrations of ropinirole in therapy of Parkinson's disease (8.3–16.5 mg/day) and restless legs syndrome (1.9–3.0 mg/day) are nausea, dizziness and somnolescence. Vomiting is also reported as a common event. Infrequently, abdominal pain, headache increased sweating and dyskinesia were reported. In rare cases, syncope in combination with sinus pause (0.5 mg/day over 2 years), sudden sleep attacks

(16 mg/day) and psychotic symptoms (6–24 mg/day) are described. Oral doses of 0.08–2.5 mg ropinirole caused a dose-related suppression of prolactin concentration. In humans, treatment with dopamine agonists is contraindicated in breastfeeding mothers, as dopamine inhibits prolactin secretion and thereby can inhibit lactation; and in pregnant women is recommended not to use ropinirole as the potential risk for humans is unknown and the available animal studies have shown possible teratogenic effects.

User safety

A user safety risk assessment which has been conducted in accordance with CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1) has been presented.

The main potential route of accidental contact with the product is dermal exposure to the product during the opening of the single-dose plastic container or during or after the administration to the dog. The possible user exposed in the first case would only be a professional veterinarian during its use in the clinic. As the product is recommended to be administered only under the direction of a veterinarian, the only situation of exposure for the pet owner would be following its administration to the dog. This exposure would be sporadic given the recommended use of the product. Accidental ocular exposure due to splashing of the product or shaking from the dog might be considered as well as a possible risk to the user, even if the possibility of its occurrence is very low.

Regarding the exposure in children, the amount of systemically available ropinirole corresponding to the scenarios of accidental ingestion via hand-to-mouth contact, dermal contact and oral ingestion of the contents of a whole single-dose container is considered to entail risk. However, since the product is recommended only to be used under the direction of the veterinarian and not be available in the home environment, it is not expected that children will have access to the product.

In relation to the type of user, special consideration must be given to pregnant or breastfeeding women. The inhibitory effect of ropinirole as a dopamine agonist on prolactin secretion has been shown in toxicity studies by the presence of oestrogen dominance in drug-treated females. Special precautions should be considered for these users, given the risk of toxicity related to prolactin secretion. Considering the latter, a specific warning (updated in compliance with the latest QRD 8.1 version and the ABCD structure defined in the relevant guidelines) is included in section 4.5 of the SPC. The extension of these precautions for women of childbearing age is deemed unnecessary.

No irritation of the skin or sensitisation potential was observed for ropinirole concentrations of up to 50%. Studies in the target species have confirmed that the product can cause moderate eye irritation in the test animals used; therefore a warning regarding the possibility of eye irritation has been included in the SPC. In addition, removal of any splashed liquid in contact with the skin or eyes has also been included in the SPC.

The calculated exposure following accidental dermal exposure of the user is well below the doses which are expected to induce pharmacological effects in humans, and most of the adverse effects reported in the toxicity studies are clearly related to the pharmacological activity of ropinirole. In addition, the possible exposure to the product will be highly infrequent given its sporadic use. It is considered unlikely that systemic adverse events will occur as a result of dermal contact with the product.

As a result of the user safety assessment, the following warnings have been included in the SPC:

- People with known hypersensitivity to ropinirole should avoid contact with the veterinary medicinal product. Administer the veterinary medicinal product with caution.

- The veterinary medicinal product should not be administered by pregnant or breast-feeding women. Ropinirole might reduce the level of prolactin due to its inhibitory effect on prolactin secretion as a dopamine agonist.
- This veterinary medicinal product can cause eye irritation. Administer the product with caution. In case of accidental eye or skin contact, rinse immediately the affected area with plenty of fresh water. If symptoms occur, seek medical advice and show the package leaflet or the label to the physician.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH Guidelines. This assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food animals. Clevor is not expected to pose a risk for the environment when used according to the SPC.

The SPC includes the following risk mitigation measures for Clevor: "Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements."

Overall conclusions on the safety documentation

Pharmacology:

Based on the data provided, ropinirole has been shown to induce emesis in dogs binding to both central and peripheral dopamine receptors. Ropinirole is rapidly absorbed after oral administration. In tablet formulation its bioavailability is about 50% in humans. However, it is nearly completely absorbed in aqueous solution. Systemic exposure in dogs via the eye revealed rapid absorption with rather low systemic bioavailability of 23%. Ropinirole related material is widely distributed in tissues and is readily able to cross the blood-brain barrier. Ropinirole is extensively metabolized; although the predominant pathway of metabolism is species-dependent. Ropinirole is excreted rapidly, mainly as metabolites and predominantly in the urine of all animal species and human. For more detailed information on the pharmacodynamic and pharmacokinetic properties of ropinirole, please see part 4 of the report.

Toxicology:

The results show that ropinirole possesses low acute toxicity after oral administration and intravenous administration in rats and after oral administration in monkeys. The main toxicological signs appear to be related with the pharmacological effect of ropinirole hydrochloride.

In rats and Cynomolgus monkeys, no major toxic effects were observed on repeated administration studies, except for centrally and peripherally mediated clinical signs related to the pharmacological effect of ropinirole. The inhibitory effect of ropinirole as a dopamine agonist on prolactin secretion was evidenced on these studies in both species, producing increased incidence of Leydig cell hyperplasia of the testis on the males and the presence of oestrogen dominance in drug-treated females in rats. However, the presence of prolactin responsive receptors in Leydig cells appear to be unique to rats and therefore the risk for hyperplasic changes in testes in other species is considered negligible. The relevant NOAEL was derived at 5 mg/kg bw/day for rats and monkeys.

Reproductive toxicity on male and female rats and mice was only seen at high doses. Developmental toxicity was only present in rats at ≥120 mg/kg bw/day, although maternotoxic signs were observed

at lower doses.

Genotoxicity and carcinogenicity:

In the Ames test performed by the applicant according to OECD GL 471, ropinirole was negative for induction of reverse mutations in the five tester strains of Salmonella typhimurium in the presence and absence of metabolic activation.

In the in vitro human lymphocyte chromosome aberration assay performed by the applicant according to OECD GL473, ropinirole did not induce biologically relevant increases in the frequency of structural chromosome aberrations, although statistically significant increases were observed at the highest tested dose for the 20-hour treatment.

The reference provided by the applicant to document the in vivo chromosomal effects of ropinirole is not consistent with the current OECD guidelines. It can be concluded that the total weight of evidence, including the overall negative in vitro assays provided in this application (Ames test and a chromosomal aberration test in human peripheral blood lymphocytes) and in published literature reports together with the absence of relevant findings in carcinogenicity studies are sufficient to conclude that ropinirole does not have genotoxic potential. This conclusion is further supported by negative studies reported in relation to the FDA's approval of ropinirole for human use (in vitro; Ames test, an HPRT gene mutation in mouse lymphoma cells, a chromosomal aberration test in human peripheral blood lymphocytes, in vivo; a mouse bone marrow micronucleus test, and most importantly, negative carcinogenic studies in rodents [only species-specific findings of neoplastic changes were indicated]).

Other studies:

Mild to moderate symptoms of eye irritation that improved 2 hours after administration and completely resolved at 24 hours post-dose have been documented for Clevor.

Ropinirole is not a skin sensitizer according to the local lymph node assay.

Due to the use of ropinirole in treatment of Parkinson's disease and restless legs syndrome, safety data from human treatment are available. The most commonly reported side effects from daily treatment were nausea, dizziness and somnolence.

User risk assessment:

The applicant has submitted a user risk assessment following the requirements of the CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1). The hazards of the formulation have been adequately described throughout the dossier. The main exposure scenarios have been identified. The main possible risks for the user have been properly identified.

Since the veterinary product under evaluation is only to be administered by a veterinarian or under their close supervision and therefore is not expected to be kept in the home environment, no additional precautions regarding children are necessary.

In addition due to the inhibitory effect on prolactin secretion of ropinirole, a risk for pregnant or breast-feeding women shall be considered. A warning measure for these users has consequently been proposed on the SPC. The extension of these precautions for women of childbearing age is deemed unnecessary.

The veterinary medicinal product is intended to be only used in non-food animals and therefore Clevor is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Pharmacodynamics

Four laboratory studies in dogs and 16 published papers were provided to describe the pharmacodynamic action of ropinirole, the pivotal emesis studies are summarised below (see table 1).

Ropinirole is a well-established dopamine agonist. It is a full non-ergot agonist at D_2, D_3 and D_4-like dopamine receptors with highest affinity for D_2. It is weakly active at the 5-HT_2, and α_2 adreno receptors, and is said to have virtually no affinity for the 5-HT_1, GABA, mAChRs, α_1 adrenoreceptors, and β-adrenoreceptors. Ropinirole does not activate the D_1 dopamine receptor and therefore does not cause dyskinesia.

The major metabolite of ropinirole in humans is N-despropyl ropinirole, also partial agonist at the hD4 receptor. N-despropyl ropinirole has lower intrinsic activity at this receptor, and was found to be a full agonist at human D_2 and D_3 receptors. The secondary human metabolite, hydroxy ropinirole (which is the principal metabolite in dogs and rats), has very low affinity and potency at all three dopamine D_2 family receptor subtypes. Ropinirole also showed selectivity for human D_3 receptors compared to human D_2 receptors in radioligand binding studies (20 fold); although selectivity was less in functional assays (10-fold). N-despropyl ropinirole had lower functional hD3 selectivity (10 fold), as compared to radioligand binding selectivity (20 fold).

Emetic effect:

Ropinirole induces emesis by activating the D_2 like receptors in the chemoreceptor trigger zone, located in the area postrema, which transmits the information to the emesis centre to trigger vomiting, see table 1 (below).

Cardiovascular effect:

In vitro: Ropinirole blocked the human ether-a-go-go-related gene (hERG)-mediated currents with the half-maximal inhibitory concentration (IC_{50}) value of 1.2 µM. In canine Purkinje fibres, ropinirole prolonged the action potential duration (APD_{90}) and suppressed the rapid delayed rectifier K^+ current (IKr) with an IC_{50} of 2.7 ± 0.25 µM (at concentrations ≥10 µM). It reduced the maximum rate of depolarization and caused depression of the plateau (at concentrations ≥30 µM), and shortened APD measured at 50% repolarization (at 300 µM) indicating a concentration-dependent inhibition of Ito, INa, and ICa. Ropinirole treatment may carry proarrhythmic risks for human patients with inherited or acquired long QT syndrome due to inhibition of IKr, especially in cases of accidental overdose or intoxication.

In vivo: The applicant presented two laboratory studies performed in 3–5 years old Beagle dogs weighing between 7–11 kg showing moderate to marked tachycardia with ocular doses of 4–23 mg/m^2 [equivalent to 0.5X-2X the recommended dose according to a Tolerance Animal Safety study, and to 1X–5X considering the dosage mentioned in section 4.9 of the SPC - 3.75 mg/m^2 (2.7–5.4 mg/m^2]; this effect on heart rate was, however, not directly dose-dependent.

Interactions / antidotes:

Ropinirole is a dopamine agonist; therefore, dopamine antagonists such as metoclopramide, domperidone, and droperidol antagonise the effect of ropinirole. Also, other antiemetics, like NK1-antagonist maropitant, might antagonise vomiting induced by ropinirole. Additionally, medication with known antiemetic properties, like antihistamines (e.g. promethazine, diphenhydramine,

dimenhydrinate, cyclizine, meclizine) or neuroleptics (e.g. chlorpromazine, acepromazine phenothiazines, butyrophenones, thioxanthenes) may diminish the effectiveness of ropinirole. Appropriate information is included in the SPC.

Development of resistance

Not applicable.

Pharmacokinetics

A large number pharmacokinetic (PK) studies have been performed in laboratory animals (including dogs) to support the human use of ropinirole (treatment of Parkinson's disease and restless legs syndrome). In those studies, ropinirole was administered orally and intravenously.

In addition, the applicant provided PK data of ropinirole (final formulation) in the target species administered via the intended ocular route, providing the plasma profiles and bioavailability of ropinirole via the ocular route. In addition, concentrations of ropinirole were determined in dog plasma in connection with 3 other non-clinical studies (dose-finding, local tolerance or safety pharmacology of ropinirole) after different ocular doses of ropinirole.

Absorption: The drug is rapidly absorbed by this route of administration with t_{max} about 10–20 minutes (depending on the sampling schedule), although the onset of vomiting may begin before reaching the C_{max}. The bioavailability is low (23%), while the oral bioavailability of ropinirole in dogs is 79%. C_{max} is dose–dependent. C_{max} values of 14.2 ± 5.3 ng/ml and t_{max} values of 15.7 ± 5.3 minutes have been reported at dose of 4.5 mg/m² and with samples collected from the cephalic vein. A dose of 5 mg/m^2 resulted in a mean C_{max} of 17.3 ng/ml and average t_{max} at 27 minutes. A dose of 10 mg/m^2 resulted in a mean C_{max} of 26–30 ng/ml. In another study C_{max} was 13.2 ng/ml at dose of 1.9 mg/m^2, 25.6 ng/ml at a dose of 3.7 mg/m^2 and 38.4 ng/ml at a dose of 7.4 mg/m^2. The t_{max} was in all of them 0.167 h (= 10 minutes).

The systemic exposure to ropinirole based on C_{max} and AUC did not show complete dose linearity as the exposure increased less than dose proportionally(AUCs from 25.4 ng.h/ml at dose 1.9 mg/m^2, still 80 ng.h/ml at dose 7.4 mg/m^2; or 24.55 ng.h/ml at dose 5 mg/m^2, still 42.65 ng.h/ml at dose 10mg/m^2).

Distribution: The distribution parameters (Vd_z, Vd_{ss}) show a wide distribution. In human, the results of population PK were approximately 7.2 l/kg with inter individual variation of 32.6%, in rats 2.0 l/kg and in monkeys 2.7 l/kg. In dogs, V_{ss} was reported to be 2.6 l/kg and V_z = 3.8 l/kg after a dose of 1 mg/kg given to 4 Beagles by a 30 minute continuous intravenous infusion. In another study, with intravenous administration to 6 Beagles as a bolus of a dose of 3.22 mg/m^2 of the diluted final formulation of ropinirole, a mean value of 1.4 l/kg was calculated for V_{ss} and 5.6 l/kg for V_z.

Metabolism: Biotransformation occurs by N-despropylation, hydroxylation and subsequent conjugation with glucuronic acid or oxidation to carboxylic acid. The predominant pathway of biotransformation is species-dependent. In dogs and rats, the main metabolite is the 7-hydroxylated metabolite. The cytochrome P450 enzymes CYP1A2 and CYP3A are responsible for the metabolism of ropinirole (in human).

Excretion: Excretion has not been studied in dogs after ropinirole administration by the ocular route. Based on the literature, the major route of excretion of ropinirole-related material is renal. In rats and dogs after intravenous administration, the portion recovered as unchanged ropinirole in the urine is only

<3% within the first 24 hours. Within the first 72 h after intravenous administration in dogs, 50.4% of the radioactive dose is excreted in the urine. A value of terminal half-life ($t_{½}$ λ) 6.37 ± 1.17 h was obtained when ropinirole was administered to 6 Beagle dogs at a dose of 7.4 mg/m^2. By intravenous route, as a bolus dose of 3.22 mg/m^2, the following values were obtained: $t_{½\lambda}$ 4.08 ± 1.61 h and a total plasma clearance of 1.02 ± 0.21 l/h/kg.

Potential for pharmacokinetic interactions:

Although ropinirole is metabolised by cytochrome P450 (CYP) enzymes in humans, and assumed to do so in dogs as well, no pharmacokinetic interactions between ropinirole and any other drug are anticipated. Polymorphisms between dog breeds make identification of sub-groups as "poor metabolisers" or "extensive metabolisers" difficult, and metabolism of ropinirole could differ between breeds.

An impact of ropinirole on the effect of other drugs is unlikely e.g. general anaesthesia for a dog after the administration of ropinirole. The effect of pre-anaesthetic tranquilizers, which act on D_2 receptors (such as phenothiazines like acepromazine, chlorpromazine, etc) may be reduced when administrated at the same time as ropinirole, but the concentrations of ropinirole are low and decrease rapidly (at 2 hours it is 25% of C_{max} and at 4 hours approximately 10% of C_{max}), and therefore its effect should be negligible. Other pre-anaesthetics have no effect on the D_2 receptors, therefore there are no expected interactions.

Possible impact of other compounds on the effectiveness of ropinirole:

Both induction and inhibition of metabolising enzymes could have major impact on the elimination and concentration in plasma, i.e. systemic exposure, of ropinirole. However, since administration of ropinirole will only occur very occasionally, it is not expected that ropinirole would produce a process of enzyme induction. The effectiveness of the drug in triggering emesis seems to depend mostly on the (rate of) absorption and local exposure. Hence, any interference by other compounds towards the metabolising enzymes would have a minimal impact on the effectiveness.

Table 1: *(preclinical data in dogs)*

Study reference	**Dose (mg/m^2)**	**Results for vomiting**			**PK data**
		Time to vomit (induction time), (min)	Occasions	Duration (min)	
Study A	5 mg/m^2 10 mg/m^2 23 $mg/m^{2\sim}$ (10+13mg/m^2)	6.8 4.8 4.8	6.8 9.8 9.5	23.5 23.5 36	C_{max}: 17 ng/ml 26 ng/ml 36 ng/ml The t_{max} was longer after the repeated dose (large variation within each dose level).
Study B	50 µg/kg bw 100 µg/kg bw 200 µg/kg bw	6.7 4.8 4.7	*Fasted (fed)*: 6.3 (2.3)	*Fasted (fed)* 20.5 22.5 (12.3) 26.3	100 µg/kg bw: $t_{max:}$ 9.6 min, C_{max} 137.4±129.25 ng/ml
Study C	4 mg/m^2	3.7 (1-6)			C_{max} : 14.2±5.3 ng/ml t_{max} 15.7±5.3 min
Study D	1.9 mg/m^2 3.7 mg/m^2 7.4 mg/m^2 7.4 mg/m^2				T_{max} : 0.167 to 1 hours. C_{max} : 13.2, 25.6, 38.4, and 34.2 ng/ml, resp.

Dose finding

The results of the pre-clinical studies (see table 1, above) with healthy laboratory Beagle dogs indicated that ropinirole administered ocularly as a solution at doses of 50, 100 and 200 µl/kg bw into the eyes (corresponding to 1.0–4.5 mg/m^2) induced emesis in all dogs on average within 5–7 minutes after administration. Based on these results, the applicant conducted two dose-finding studies in clinically healthy dogs; under clinical conditions one positive controlled and one uncontrolled study.

Dose-finding study – positive controlled (apomorphine)

In the first dose-finding study doses of 1, 2 or 4 drops of the investigational product with a strength of 30 mg/ml and drop size of approximately 27 µl (dose range 28–220 µg/kg, corresponding to 0.9, 2.5 and 5.5 mg/m^2) were studied in an open, randomised, dose-escalation, positive-controlled study, including 20 dogs (14–32 kg). All dogs (n=20) were initially treated with apomorphine (positive control), and after appropriate wash-out periods treated with the (increasing) doses of ropinirole. If a dog vomited within 10 minutes after administration, no further ropinirole doses were given; otherwise, the dog continued to the higher dose level.

The objective of the study was to find efficient and tolerable doses of ropinirole to induce vomiting in dogs within a reasonable time. The primary end point was whether or not a dog is vomiting within

10 minutes after treatment administration. Ropinirole was administered as eye drops (30 mg/ml) at a dose ranged of 2.5–5 mg/m^2, and compared to apomorphine efficacy (subcutaneous administration, 0.10 mg/kg) at different time points. According to the study protocol, dogs should not receive a higher treatment dose with the test product, if emesis was induced.

Efficacy: The results of this study indicated that correlation of weight of the dog and dose of ropinirole-induced emesis was not conclusive. However, there was a trend that larger dogs (over 25 kg) did not vomit with the smallest tested dose, but only when the dose was increased. Further, on individual level dose response, emesis was in general induced more rapidly with higher doses. Considering the ocular dosing route and its proximity to the site of action of ropinirole in the brainstem, it can be anticipated that the effect is not linear and that an effective dose would be better correlated to the body surface area than to the body weight. As a consequence, a relatively lower dose would be considered sufficient for heavier dogs. On basis of a post hoc analysis of the relationship between the dose given (expressed as mg/m^2 body surface) and response to treatment, the applicant concluded (as detailed below) that a sufficient response rate was reached at doses of 2.5–5 mg/m^2 body surface.

At 10 minutes after drug administration, the number of vomiting dogs increased when the dose of ropinirole increased. The responder rate was 15% (3/20), 44% (7/16) and 44% (4/9) after administration of 1, 2 and 4 drops of ropinirole, respectively, and 80% (16/20) after administration of apomorphine. The difference between ropinirole and apomorphine was statistically significant for 1 drop ($p < 0.001$) and 2 drops ($p=0.045$), while 4 drops did not differ significantly from apomorphine ($p=0.190$). The responder rate of ropinirole (74%, 14/19) was comparable to that of apomorphine (80%, 16/20) when all ropinirole doses (1–4 drops) were combined. When vomiting within 20 minutes was considered, 2 drops of ropinirole solution were comparable to apomorphine [for ropinirole 89% (17/19) and for apomorphine 90% (18/20)].

In total, 95% of dogs treated with ropinirole vomited at a dose up to 5 mg/m², and 79% at a dose of less than 2.5 mg/m². Moreover, 89% of treated dogs vomited in 20 minutes at a dose of less than 5 mg/m² (at times of 10 minutes, 20 minutes and 30 minutes, ropinirole responders were 74%, 89%, 95%, respectively) and 68% at a dose of less than 2.5 mg/m² (84% with the dose smaller than 2.7 mg/m², i.e. 110 µg/kg bw).

There are flaws in the interpretation of the statistical analyses. The applicant has drawn the following conclusion regarding 2 drops of ropinirole: "The difference in the responder rate between 1 drop of ropinirole and apomorphine was statistically significant ($p=0.001$), while the responder rate for 2 drops ($p=0.505$) and 4 drops ($p=0.656$) did not differ significantly from apomorphine, indicating that 2 drops is sufficient to induce vomiting within 20 minutes in dogs weighing 14–32 kg". Nevertheless, this analysis is not relevant. The most relevant analysis was the one where all dosages (1–4 drops of ropinirole) were combined.

Tolerance: Local tolerance and clinical safety of the product were good. Systemic adverse events associated with the product seem to be acceptable as only 4 dogs (20%) experienced mild adverse events (AEs), with diarrhoea most commonly reported. No AEs were reported after the administration of the active control, apomorphine. The heart rate was examined only 2 hours after treatment, so the peak effect, which occurs 20–30 minutes after treatment, was not assessed. Although it is accepted that no adverse events related to circulation was noted in the study it is regarded a draw-back that the effect on the heart was not sufficiently explored in this study. Local adverse events in the eye were very common, consisting of hyperaemia, protrusion of the third eyelid and conjunctival discharge. Although the clinical signs were transient, the common occurrence and the potential pain they may cause is a concern, and the reactions have been addressed in the SPC.

The results indicate that ropinirole was efficacious at a single dose of 2.5 mg ropinirole/m² body surface to induce vomiting (74%, 89% and 95% of dogs vomited within 10, 20 and 30 minutes); however, efficacy was lower than the reference compound used (apomorphine: 80%, 90% and 100%, respectively). Metoclopramide as rescue treatment was necessary to be administrated in one case of extended vomiting caused by ropinirole, according to investigator judgement (whereas it was not considered necessary in one dog affected from extended vomiting that received the reference product). Ropinirole also induced other mild AEs, which were not reported for the reference product, however, a significant limitation of the reference compound is the lack of ability to repeat dose for non-responders.

Based on the results of this study, the applicant considered that for further studies, a single dose of 2.5 mg ropinirole /m² body surface was planned to be administered. However, as the dose response was not conclusive in this study, and also did not include dogs of higher and lower weight, an additional dose-finding study was conducted to test the efficacy and safety of a minimum single dose (initial dose) of 2.5 mg/m² of ropinirole eye drops in dogs to induce vomiting.

Dose-finding study – uncontrolled

The study included 30 healthy dogs of any breed and between 2.5–4 kg (small breed) to 40–80 kg (large breed). Primary endpoint was whether or not a dog vomited within 30 minutes after the first treatment administration. Small dogs received 1 drop of ropinirole (30 mg/ml solution) into the left eye, and an additional dose, 1 drop in the right eye, if the dog had not vomited within 30 minutes. Large dogs were randomised equally to receive 4 or 6 drops (30 mg/ml strength) or 4 drops (using a 50 mg/ml strength), stratified by the following body weight groups: 40–53, 53–65 and 65–80 kg. The dog received an additional higher dose if vomiting did not occur within 30 minutes. The additional higher dose was 1 drop more than the initial dose. 4 drops were equally divided in both eyes, while doses from 5 to 7 drops per single administration were divided into 2 smaller doses given at 2 minute intervals.

Ropinirole was effective to inducing vomiting at doses of 2.6 to 4.5 mg/m^2 in small and large dogs. 93% vomited within 17 minutes after administration, and the rest vomited after receiving an additional dose. The target dose of ropinirole 3.75 mg/m^2 with a dose range of 2.7–5.4 mg/m^2 was selected for the confirmatory clinical study.

In this study one dog was treated with antidote (metoclopramide) as it had been vomiting 23 times for 58 minutes. After antidote treatment it stopped vomiting. The study confirmed the efficacy of ropinirole eye drops to induce vomiting in dogs with the target dose of 3.75 mg/m^2 (95% dogs vomited within 30 minutes after initial administration of the product). An additional dose can be given 15 to 20 minutes after the administration of the initial dose, which was well tolerated.

The correct dosing increases the efficacy of the product, and dogs receiving a high dose start usually vomiting sooner than dogs receiving a low dose. However, the number of vomits or duration of vomiting were not related to the dose.

Target animal tolerance

One pivotal GLP-compliant target animal safety study, and also the results of two non GLP-compliant preclinical and dose finding studies were provided to investigate target animal safety of the product. In addition, safety data obtained from the clinical trial and published literature references were considered.

Pivotal target animal safety study

The pivotal target animal safety (TAS) study was performed in line with GLP requirements, and according to the requirements of the VICH Topic GL43 Guideline on Target Animal Safety for Veterinary

Pharmaceutical Products (EMEA/CVMP/VICH/393388/2006). The applicant used different doses (with the highest tested doses up to 5 times the maximum clinical dose, for three days) and determined the adverse effects on the target animal (dog) focusing on eye irritation and cardiovascular safety.

Results showed that ropinirole induced emesis in dogs, its indication, with adverse effect in eyes and heart. The typical clinical signs are very similar in all (non)clinical studies and relate to the pharmacological action of ropinirole (dopamine agonists specially D_2 agonist), consisting mainly of signs of nausea (salivation, vomiting, retching, laboured or exaggerated respiration), dopaminergic central nervous system signs (lethargy, somnolence, decreased activity, ataxia or uncoordinated movements, muscle tremors) and local eye symptoms (conjunctival hyperaemia, ptosis or blepharospasm, ocular discharge). Most of the reported clinical signs were mild or moderate and all of them transient in nature. Based on study results, protracted vomiting (which can be considered to start 45–60 minutes after dosing) can be effectively discontinued by using specific D_2 antagonists (metoclopramide).

No treatment-related effects on physical examination, body weight, haematology, clotting, clinical biochemistry, urinalysis, organ weights, macroscopic pathology or histopathology of examined tissues were noted in the TAS study.

Tachycardia has been reported in all the studies where the heart rate has been evaluated as a parameter. Slight to moderate tachycardia has been recorded at clinical and subclinical doses. The peak values of heart rate occur at the same time as peak of emetic episodes (10–20 minutes after ophthalmic dosing), which is usually before the maximum plasma concentrations are reached. Increase in heart rate is considered to be induced by the chronotropic effect induced by nausea and vomiting given that ropinirole has negligible affinity for adrenoreceptors and, therefore, it is unlikely that would cause tachycardia by a direct action.

The effects of ropinirole eye drops on blood pressure were minimal, and restricted mainly to the systolic pressure. Decrease in blood pressure is considered to be a direct effect of ropinirole via D_2 receptors causing vasodilation, which causes a drop in blood pressure.

However, some deficiencies were noted in the study design of the TAS study, as individual data from the physical examinations (signs of conjunctivitis, keratitis and ocular discomfort) were only gathered on day 1 and 3. The ophthalmoscopic examination was only performed pre-treatment and 4 days after treatment with ropinirole, although examinations were carried out by experienced veterinary ophthalmologists. The applicant claims that no treatment-related effects on ophthalmoscopy parameters were noted. Corneal opacity recorded in some dogs is claimed by the applicant not to be treatment-related but a common finding in dogs of this age, which are housed and treated under the conditions in this study. To allow a proper assessment of local reactions in the eye, the applicant has compiled adverse event data including an evaluation of a potential dose effect relationship. These local signs are associated primarily with the pharmacological action (local activation of dopamine receptors in the eye) of ropinirole. Additionally, the potential occurrence of permanent injuries to the eye is discussed given that the product is administered to a healthy eye and a respective warning has been included in section 4.5 of the SPC.

Monitoring of heart rate was only performed before each administration of ropinirole, and 1 and 6 hours after the first administration on day 2. As compared to placebo, an increased heart rate was observed in the ropinirole group from the time before treatment up to one hour after administration. Since an earlier non-GLP study clearly demonstrated that an increase in heart rate peaks about 20–30 minutes after treatment, the selected time point for measuring heart rate in the TAS study was not optimal to assess treatment related cardiac effects. Furthermore, it would have been useful to have information

about the heart rate for all the dogs at all three days of treatment, not only for one treatment at one day out of the 6 treatments that were executed on 3 following days.

Results from other studies:

The findings of the pivotal TAS study (reactions on eyes and heart) were in line with observations from other preclinical and clinical studies presented in the dossier. In these studies, the examination of the eyes was however not executed with ophthalmoscopy implying that some local reactions might have passed unnoticed. No fluorescein staining was performed of the treated eyes which would have been useful in order to determine potential local reactions of cornea.

Local tolerance of the final formulation, as well as other near-final tested formulations used in non-clinical studies, was limited to the investigation of conjunctival hyperaemia, ptosis or blepharospasm, and ocular discharge. However, to allow a clear conclusion on local tolerance the applicant has presented a table including abnormal eye symptoms recorded during physical examination where it can be observed that the majority of the animals had a mild scoring for all the symptoms (already reflected in the relevant section of the SPC) when the product is administered at the recommended dose.

In a laboratory study, different doses tested on the same individuals (5, 10 and 23 mg/m²) induced relatively similar increases in heart rate. In average, a maximum heart rate of 145–160 beats (b) per minute was reached 10-25 minutes after ocular administration of 5–10 mg ropinirole/m². The average increases compared to the baseline values were +53–60 b/min, respectively. Slight (+19 mmHg at highest), short term initial increase in systolic blood pressure (SAP) was seen within 5 minutes after ocular dosing. Approximately 9% increase in QTc interval, corrected by Fridericia formula, was seen in all doses of ropinirole in comparison with the corresponding time point in an untreated control group.

In another study, the recommended dose of approximately 4 mg/m² showed a clear increase in heart rate after dosing of the test medication. On average, the maximum heart rate of 192 b/min was reached within 10 minutes, with an average increase of +108 b/min. Tachycardia ameliorated slowly after peak value but, at the end of the 30 minutes measuring period, was still increased (+60 b/min) when compared to the baseline value.

The plasma exposures correlated well to the doses in both studies; the differences in the effects are possibly a result of variation in individual response of the study animals. The maximum heart rate was reached in 10–20 minutes after dosing, and lasted approximately 20 minutes (the duration of the effect is seen from 10–20 minutes until 40–50 minutes after dose).

Possible QT-time prolonging properties of ropinirole were analysed in electrocardiogram (ECG) using commonly used heart rate correction formulas (Fridericia and Van de Water). No prolongation in QTc-time was recorded in these studies.

In order to analyse the impact of transient ropinirole induced tachycardia in dogs (and specifically in undiagnosed heart disease), the applicant has provided a detailed review regarding heart rate regulation in dogs (related to blood pressure, blood pressure regulation, and nausea and emesis), physiologic background of the QT interval in dogs (including pathologic alterations in this interval and pathologic heart rhythms) and effects of tachycardia (in the normal heart and in heart failure). Cardiac effects of ropinirole (including cardiac pharmacodynamics and clinical cardiac effects) were exposed as well as cardiovascular effects of ropinirole in common heart diseases (chronic valvular heart disease, myocardial disease, cardiac arrhythmias and congenital disease). Additionally, an assessment of the use of ropinirole in the undiagnosed above-mentioned specific heart diseases has been provided.

Based on this review, available data indicate that Clevor is safe in dogs with heart failure, and that its risk-benefit ratio for dogs with both undiagnosed and diagnosed heart disease is positive. However, a warning of caution in dogs with heart disease has been added to the SPC: "This veterinary medicinal product may cause a transient increase in heart rate up to 2 hours after administration. The safety of the product has not been studied in dogs with diagnosed cardiac disease/dysfunction. Use only according to the benefit-risk assessment by the responsible veterinarian."

Moreover, the use of ropinirole has neither been studied during pregnancy and lactation nor in elderly dogs, and respective information is included in the SPC.

Based on the findings of the studies submitted, it can be concluded that ropinirole at the recommended dose of 30 mg/ml (eye drop, solution) is associated with signs of nausea, lethargy and tachycardia and local eye symptoms. Appropriate warnings have been included in the SPC and product literature.

Table 2: *Tolerance of ropinirole*

Study reference	**Dose**	**Results**
Target animal safety study in the Beagle dog N=24	0 mg/ m^2/day, 8.5–10.6 mg/m^2/day 35.2–40.9 mg/m^2/day 49.5–58.9 mg/m^2/day (equivalent to 0 mg/kg/day 0.45–0.62 mg/kg/day 1.88–2.36 mg/kg/day 2.56–3.29 mg/kg/day) i.e. 0X, 1X, 3X and 5X the maximum clinical dose.	No mortality occurred. **Clinical signs** (salivation, vomiting of mucus, retching, lethargy, tremors, hunched posture, ventrolateral recumbency, laboured respiration, discharge from the eyes, ptosis and general erythema of the mucous membranes of the eyes) in all groups. Comparable in frequency and severity between the 1X, 3X and 5X dose groups. Slight hyperaemia was noted in individual animals of all groups. The following findings were observed incidentally at 6 hours after dosing: slight conjunctival discharge, slight to moderate swelling, slight to severe blepharospasm and slight protrusion of the third eyelid. Findings were noted in ¼ females of the 1X dose group, ¼ males and ¼ females of the 3X dose group and ¼ males and 2/4 females of the 5X dose group. **Food consumption** was decreased in individual animals of the 1X, 3X and 5X dose group but no treatment related effects were noticed on **body weights**. **Ophthalmologic examinations**: no treatment-related effects including Schirmer tear test, intra ocular pressure and fluorescein staining test were noted. An increased mean **heart rate** and a decreased mean systolic **blood pressure** were noted at 1 h after dosing in all dose groups. At 6 hours after dosing, values were comparable to pre-test and/or pre-dose. Changes in heart rate and rectal temperature in each animal were considered within normal biological variation. No treatment-related effects on **haematology, clinical biochemistry, urinalysis, necropsy**
	Ropinirole 30 mg/ml eye drops, solution.	

		and **organ weights** were noted. All **histologic** changes were considered to be incidental findings.
Local tolerance and safety pharmacology in the Beagle dog N=4	5, 10 and 10+13 mg/m^2 corresponding to max. 540+680 µg/kg bw Ropinirole 50 mg/ml eye drops, solution. 5 mg/m^2 x 2 Formulations: Ropinirole 30 mg/ml solutions with different excipient compositions.	Mild **eye irritation**, resolving in 4 hours. Nausea, intermittent shivering and hypoactivity. **Vomiting** was slightly more intensive and lasted longer with higher doses, but no clear dose-correlation could be seen. Moderate increase in **heart rate** with all tested doses of ropinirole. Effects noted on the QT interval were not considered to be medication-related but a consequence of changes in heart rate by induced vomiting.
Preliminary cardiovascular safety of Ropinirole; solution dosed into eyes of the Beagle dog N=7	200 µg/kg bw corresponding to 3.8–4.5 mg/m^2 (approximately 4.0 mg/m^2). Ropinirole 30 mg/ml solution.	**Nausea** and mild symptoms of **eye irritation**. Conjunctival hyperaemia and mild blepharospasm appeared soon and continued during the whole 30 minute recording period, resolving after 2 hours post dosing. Increase in **heart rate** with the maximum heart rate within 10 minutes (192 bpm). Tachycardia ameliorated slowly after peak value and, at the end of the 30 minute recording period, the increase was still +60 bpm when compared to the baseline value. Increase in **blood pressure** within 5 minutes after dosing. QTc interval remained within the normal variation (230–249 ms), whereas QTc interval was slightly decreased (max -11 ms).

Clinical studies

Dose confirmation

The application had been granted MUMS/limited market status, and the CVMP accepted the absence of any dose confirmation studies as adequate dose determination and field studies had been submitted.

Field study

The applicant conducted one randomised, double- blind, parallel-group, placebo-controlled multicentre clinical field trial to confirm the dose, the efficacy and the clinical safety of ropinirole, and to evaluate the usability of the product.

In the pivotal clinical field study, the product was compared with a placebo, not a positive control, in order to ensure the blindness of the study.

The applicant selected the primary efficacy endpoint in the pivotal clinical field trial (induction of vomiting within 30 minutes after initial administration) based on the need for a quick onset of effect; this timeframe is supported by findings in literature.

The animals included in the clinical pivotal field study were healthy client-owned dogs, which were not in need of emetic treatment. However, for the proposed indication (induction of vomiting), this is considered acceptable, especially considering that the Clevor group was compared with a placebo group, and the use of placebo in dogs in a critical situation would not be considered ethical.

Tolerance:

This study was performed in healthy dogs with healthy/normal eyes. However, in dogs with an abnormal shape of the eye lids or palpebral fissure, which might have caused chronic ocular changes, this could alter the efficacy and safety of Clevor. Some chronic ocular changes could potentially affect the conjunctiva, where ropinirole is absorbed. Because of that, a precaution for use has been added to the SPC section 4.5 Special precautions for use: "The safety and efficacy of the product have not been studied in dogs with ocular disease or injury. In case of a pre-existing ocular condition with clinical signs, use the product only according to the benefit-risk assessment by the responsible veterinarian."

Dogs included showed during the 30 minute treatment period different clinical signs such as lethargy and nausea. Adverse events were assessed as mild or moderate (tachycardia, diarrhoea and extended duration of emesis). Even if tachycardia could be related to the vomiting process, the direct effect of the drug on the autonomic nervous system seems to be likely, taking into account the prolonged increase of heart rate. Besides, one dog may have had a drug induced hepatopathy.

Conclusions:

In the clinical field study, the efficacy of ropinirole at the recommended dose of 3.75 mg/m² was investigated in healthy dogs, and compared to placebo. 95% (ITT) and 100% (PPP) of treated dogs vomited within 30 minutes after administration of the eye drops (primary endpoint). Vomiting started approximately 11–12 minutes after administration of the drop(s), and lasted approximately 23 minutes.

Common adverse events noted in the treated dogs were mild or moderate tachycardia and diarrhoea, and extended duration of emesis (more than 60 minutes). Although tachycardia could be related to the vomiting process, a direct effect of the drug on the autonomic nervous system seems also to be likely, taking into account the prolonged increase of heart rate. Metoclopramide (0.5 mg/kg s.c.) was used as rescue medication in 5 out of the 8 dogs with an extended duration of vomiting (more than 60 minutes), as considered necessary by the investigator (this effect was also seen in the dose findings studies, i.e. one out of 20 dogs in one study, one out of 30 dogs in another).

The results also indicated that 95.5% of dog owners assessed administration of the product as "very easy" or "easy", and the applicant also applied that the product should be prescribed by a veterinarian to be administered by an animal owner at home, when needed. The applicant justified this with the need for rapid action in case of certain intoxication, and only in close liaison with the prescribing veterinarian whose advice should be sought by telephone. Such distribution and administration by the dog owner should be carefully considered by the veterinarian, i.e. only for dogs with a known history of intoxications requiring treatment with an emetic substance, and only if dogs did not show any clinical signs of intoxication at the time of administration. The CVMP acknowledged the need for quick treatment in certain situations; however, the Committee also considered that dog owners might not be appropriately trained to recognise possible signs of intoxication in a dog, or take appropriate action in

case of adverse reactions, and close liaison with the prescribing veterinarian might not always be performed or be possible. By recommending the use of ropinirole by the owner instead by trained veterinary professionals, the health of a treated dog might be at risk; even when consulting a veterinarian via phone. Clevor should therefore only be administered by a veterinarian or under their close supervision.

Overall conclusion on efficacy

Pharmacodynamics:

Ropinirole is a well-established active substance in human medicines (dopamine agonist used in anti-Parkinson medicines). Ropinirole primarily activates dopamine D_2 and D_3 receptors to induce emesis in dogs. In vitro and in vivo data showed that ropinirole in dogs can have cardiovascular effects, resulting in vivo in moderate to marked increase in heart rate, short term initial increase in systolic blood pressure, and an increase in QTc interval.

Interactions:

Ropinirole is a dopamine agonist; therefore, dopamine antagonists such as metoclopramide, domperidone, and droperidol do antagonise the effect of ropinirole. Also, other antiemetics, like NK1-antagonist maropitant, are expected to antagonise vomiting induced by ropinirole. Additionally, medication with known antiemetic properties might reduce the effectiveness of ropinirole.

Pharmacokinetics:

Ropinirole after ocular administration to Beagle dogs at different dose levels was rapidly absorbed with t_{max} about 10-20 minutes, although the onset of vomiting may begin before reaching the C_{max}. The bioavailability following ocular administration is low (23%). C_{max} is dose–dependent; a dose of 5 mg/m^2 (approximately the proposed therapeutic dose) resulted in a mean C_{max} of 17.3 ng/ml and average t_{max} at 27 minutes.

The systemic exposure to ropinirole based on C_{max} and AUC did not show complete dose linearity as the exposure increased less than dose proportionally. The distribution parameters (Vd_z, Vd_{ss}) show a wide distribution in dogs, as in others species studied. Based on literature data, the major route of excretion of ropinirole is renal.

Target animal safety (TAS):

Tolerance was investigated in a pivotal TAS study, supported by some pre-clinical studies and the field study. The typical clinical signs observed at all dose levels (1x, 3x and 5x RTD) are very similar in all (non)clinical studies and relate to the pharmacological action of ropinirole (dopamine agonists, especially D_2 agonist), consisting mainly of signs of nausea (salivation, vomiting, retching, laboured or exaggerated respiration), dopaminergic central nervous system signs (lethargy, somnolence, decreased activity, uncoordinated movements, muscle tremors) and local eye symptoms (conjunctival hyperaemia, ptosis or blepharospasm, ocular discharge). Most of the reported clinical signs were mild or moderate and all of them transient in nature.

An emetic medicine ideally should not provoke persistent and prolonged vomiting. However extended vomiting (more than 60 minutes) was noted in three studies, and in some cases metoclopramide (0.5 mg/kg s.c.) was needed as rescue medication: one out of 20 dogs one study, one out of 30 dogs in another and 8 out of 100 dogs in a third (5 of these needed recue treatment). The success in antagonising extended vomiting was obtained in all cases.

The use of ropinirole has neither been studied during pregnancy and lactation nor in old dogs, or in dogs with existing cardiac disease. Appropriate warnings have been included in the SPC and product literature.

Dose finding:

Two dose finding studies in clinically healthy dogs were provided, one positive (apomorphine) controlled and one uncontrolled study.

A study tested ropinirole eye drops to inducing emesis in dogs at a dose of 28–220 µg/kg bw (corresponding to 0.9, 2.5 and 5.5 mg/m^2, or 1, 2 or 4 drops). The effective dose was better assessed using body surface area than body weight, with a dose range of 2.5–5 mg/m^2. After receiving ropinirole, 74%, 89% and 95% of dogs vomited within 10, 20 and 30 minutes, whereas 80%, 90% and 100% of dogs treated with apomorphine vomited, respectively. The results indicate that ropinirole had slightly less efficacy than the reference compound used (apomorphine), induced mild adverse reactions (not reported for the reference product), and also extended vomiting in 1 ropinirole-treated dog (which required the use of metoclopramide as an antidote).The applicant considered that a single dose of 2.5 mg ropinirole /m² body surface was effective; however, as the dose response was not conclusive in this study, an additional dose-finding study was conducted.

In another dose-finding study ropinirole at a dose of 3.75 mg/m^2, ranging doses from 2.6 to 4.5 mg/m^2, was effective to induce vomiting in small and large dogs (93% vomited within 17 minutes after administration, and the rest (n=2) vomited after receiving an additional dose). In this study, adverse events were reported in 28 dogs (93.3%) and their severity was considered as mild (eye redness, protrusion membrane nictitans, lethargy and other unspecified eye disorders). Increases in heart rate were also commonly detected. Based on the results of this study the target dose of 3.75 mg/m^2 with a dose range of 2.7–5.4 mg/m^2 was selected for the pivotal clinical field study.

Field study:

In the pivotal field study, the efficacy of ropinirole eye drops (30 mg/ml) at the recommended dose of 3.75 mg/m² compared to placebo was investigated in 132 healthy dogs. Ropinirole induced vomiting in dogs at a target dose of 3.75 mg/m^2 with a responder rate within 30 minutes (95% of tested dogs). The initial target induced vomiting in 87% of the dogs, and when an additional dose was administered to the remaining animals (13%), vomiting was induced in 62% of them. There was a relationship between the onset of vomiting and the dose, but not between the duration of vomiting and dose or between the number of vomits and the dose. Vomiting started approximately 11–12 minutes after administration of the drop(s), and lasted approximately 23 minutes.

The usability of the product was stated as one secondary objective of the field study. The results indicated that 95.5% of dog owners assessed administration to be "very easy" or "easy", and the applicant proposed that the product could be prescribed by a veterinarian to be administered by an animal owner at home, when needed. The CVMP acknowledged the need for fast induction of emesis for certain types of intoxication in dogs. However, the CVMP also considered that the decision to induce vomiting in a dog must in each case be based on a veterinary diagnosis. The applicant's proposed recommendations in the product literature (e.g. for the dog owner to consult a veterinarian by telephone prior to the use of Clevor) could not replace a proper veterinary diagnosis. In addition, the use of the product is associated with common adverse reactions (extended vomiting), which might require veterinary intervention. The CVMP therefore considered that due to the contraindications and precautions listed in the SPC, it is not appropriate for the veterinary medicinal product to be made available to the animal owner for use in the home. The CVMP therefore concluded that the product should only be administered by a veterinarian or under their close supervision

Part 5 – Benefit-risk assessment

Introduction

Clevor is an eye drop solution for dogs containing ropinirole (as the hydrochloride). The active substance is well-known from its use in human medicine for the treatment of Parkinson's disease and restless leg syndrome. However, ropinirole has not previously been authorised for use in veterinary medicine in the EU.

Ropinirole is a dopamine D_2 receptor agonist. The product is intended for use in dogs for the induction of vomiting. The proposed effective dose is 3.75 mg/m^2 body surface (2.7–5.4 mg/m^2, equivalent to 1–8 eye drops depending on the size of the dog), administered by the ocular route, as a single dose (an additional dose may be given 15 to 20 minutes after administration of the initial dose).

Clevor is innovative because ropinirole is a novel active substance in veterinary medicine, and because of its route of administration, that is, ocular, for the induction of vomiting.

The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application).

The product has been classified as MUMS/limited market and therefore reduced data requirements apply that have been considered in the assessment; i.e. the provision of the process validation scheme instead of production scale validation data, and the absence of dose confirmation studies.

Benefit assessment

Direct therapeutic benefit

The proposed direct benefit of Clevor is its efficacy in the induction of vomiting, which was investigated in dogs in two dose finding studies, and one field study conducted to an acceptable standard. The clinical trial showed that 95% of dogs vomited within 30 minutes after administration of the eye drops in accordance with the recommended dosing instructions.

Additional benefits

The product provides a new route of administration of an emetic medicine for dogs, and would increase the range of available treatment options.

Risk assessment

Main potential risks have been identified as follows:

Quality:

Information on development, manufacture, control and stability 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.

Safety:

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

Administration of Clevor in accordance with SPC recommendations is generally well tolerated. Very commonly reported adverse reactions include lethargy and increase in heart rate, as well as local eye reactions (hyperaemia of the eye, ocular discharge, protrusion of the third eyelid, blepharospasm) and commonly reported reactions at the eyes (swelling, itching of the eyes), tachypnoea, diarrhoea, and extended duration of vomiting (more than 60 minutes), which might require a rescue medication (antiemetic).

Risk for the user:

Clevor can produce eye irritation and therefore appropriate safety advice is included in the SPC.

Clevor can pose a risk to pregnant or nursing women given the inhibitory effect on prolactin secretion of ropinirole, and specific measures are necessary to mitigate the risk. The extension of these precautions for women of childbearing age is deemed unnecessary.

Since the product should only be used under the direction of the veterinarian exposure of children to the product is not anticipated to occur.

Risk for the environment:

Clevor is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk management or mitigation measures

User safety:

User safety risks have been identified, mainly the risks associated with the eye irritation potential of the formulation, and risks associated with exposure in pregnant or nursing women. These risks have been addressed by the safety warnings in the SPC.

Environmental safety:

Standard advice on waste disposal is included in the SPC: "Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements".

Restriction in the use of the product:

The applicant applied for the product to be used by the animal owner at home. However, the CVMP considered that this would put the health of the majority of dogs to be treated at unnecessary risk, and concluded that the product should only be administered by a veterinarian or under their close supervision. The sentence "The veterinary medicinal product should only be administered by a veterinarian or under their close supervision." has been included in section 4.9 of the SPC.

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: "Induction of vomiting in dogs." The product has been shown to be efficacious to induce emesis in dogs, and the CVMP agreed to the following indication(s): "Induction of vomiting in dogs."

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Clevor 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.