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Veterinary Medicines and Product Data Management

Scientific discussion

This module reflects the initial scientific discussion for the approval of Cimalgex (as published in July 2011. For information on changes after this date please refer to the document "Changes since initial authorisation of medicine".

1. Summary of the dossier

Cimalgex is eligible for assessment under the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 as it contains a new active substance which has not been authorised in the Community for use in a medicinal product intended for use in animals.

The active ingredient, cimicoxib, is a specific inhibitor of cyclo-oxygenase-2 (COX-2) and is a non steroidal anti-inflammatory drug (NSAID) of the coxib family.

Cimalgex tablets contain cimicoxib (8 mg, 30 mg and 80 mg) and are presented in packs/containers of 8, 32, 45 or 144 tablets. The route of administration is oral, and the target species is dogs. Cimalgex tablets are indicated for use in dogs, for the relief of pain and inflammation associated with osteoarthritis and also for the management of peri-operative pain due to orthopaedic or soft tissue surgery.

2. Quality assessment

Composition

Cimalgex tablets are presented in three different strengths, containing 8 mg, 30 mg and 80 mg cimicoxib respectively. The different strengths are compressed from a common blend tabletting mix in which the active substance comprises 7.27% w/w.

Well established pharmaceutical grade excipients are used in the manufacture of the tablets, lactose monohydrate (serving as the diluent), povidone K25 (binder), crospovidone (disintegrant), sodium laurilsulfate (wetting agent), macrogol 400 (hydrophilic polymer) and sodium stearyl

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fumarate (lubricant). A flavouring agent which has been used previously in several authorised veterinary medicinal products (pig liver powder) is included to achieve palatability of the tablets.

Containers

The finished product is presented in aluminium blisters, which are then packed inside a cardboard carton, or in child-resistant containers made of high density polyethylene (HDPE) with polypropylene (PP) caps.

Development Pharmaceutics

The three strengths of Cimalgex tablets (8, 30 and 80 mg) have been developed for the treatment of dogs of 4 kg, 15 kg and 40 kg average bodyweights, respectively. The tablets contain a new active substance, cimicoxib, but all the excipients are commonly used in this type of veterinary tablet formulation. The tablets have a score on both sides to enable breaking into, and subsequent administration of, half tablets.

The choice of the excipients has been conclusively justified.

Cimicoxib is a crystalline, white, odourless powder with a neutral taste. It is practically insoluble in water and aqueous buffers of physiological relevance. As the solubility of cimicoxib is low, and it has been demonstrated *in vivo* that the particle size of the drug substance is the critical property for drug product performance, the cimicoxib is micronized in order to achieve suitable bioavailability. The dissolution test applied is merely used as a general quality test, but it is not indicative for *in vivo* performance. The dissolution method has been developed based on the solubility characteristics of cimicoxib, to ensure sink conditions for all strengths and with the gastric pH of the dog in mind.

The applicant has provided information on the clinical batches used in the main efficacy and safety studies; the final formulation is also the clinical formulation.

Method of manufacture

The manufacturing process can be considered a standard process comprising wet granulation, mixing, drying, sieving and tabletting. Standard equipment is used. The process has been satisfactorily validated at the pilot scale. A validation plan for production scale has been provided.

Control of starting materials

Active substance

The synthetic manufacturing process of cimicoxib has been sufficiently well described, and the control during manufacture is considered acceptable. Appropriate pilot and production scale batch data have been provided.

The structure of cimicoxib has been verified by spectroscopic methods and elemental analysis and is also supported by the route of synthesis. The synthesis results in only one single crystalline polymorph. The primary reference materials used in the control of the active substance have been

fully characterised. Potential impurities, including related substances and solvents, have been suitably identified and accounted for. No metal catalysts are used in the synthesis of cimicoxib.

Cimicoxib is controlled according to suitable and acceptable specifications. The analytical procedures are well described and have been appropriately validated. The assay limits are justified by batch analysis and stability data. Likewise for the specifications and limits for related substances, which are in compliance with the relevant VICH guidelines. The relevant residual solvents are also controlled to the appropriate VICH criteria. Inorganic impurities and water content are also appropriately controlled. As cimicoxib is micronized, a specification to control its particle size has been established in order to obtain adequate dissolution/absorption of the cimicoxib from the drug product. The microbiological quality of the drug substance has been evaluated for three consecutive batches and the European Pharmacopoeia (Ph. Eur.) criteria for non-sterile pharmaceutical products for total aerobic microbial count (TAMC) and total yeast and mould count (TYMC) were met.

Formal VICH and stress stability studies have been performed which demonstrate that cimicoxib can be considered a stable substance under VICH conditions. Accelerated stability studies, for up to 6 months, have been completed and long term stability data for up to 5 years are available. No significant change in any of the stability indicating parameters monitored has been observed. The results of the stability studies support the proposed retest period of 3 years, and the data demonstrate that no special storage conditions are required.

Excipients

The excipients are lactose, povidone K25, crospovidone, sodium laurilsulfate, macrogol 400 and sodium stearyl fumarate. All the excipients conform with the respective monograph of the Ph. Eur. except the flavouring agent, for which a comprehensive in house specification is applied. This flavouring is made from pig livers collected in the EU from healthy animals fit for human consumption. The livers have been controlled and released by EU official veterinary services before they are processed and ground as a powder which is sterilised by gamma-irradiation. Viral safety has been suitably ascertained.

Packaging materials

The finished product will be packaged in aluminium blisters (polyamide/aluminium/PVC - aluminium) or child resistant HDPE bottles with PP twist-off caps. All the packaging materials comply with relevant EU directives and regulations and appropriate specifications are provided. The PP caps for the bottles are child resistant; this has been ensured by acceptable certification.

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

The applicant has provided declarations from manufacturers/suppliers regarding the absence of any TSE risks as defined in the "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products". These are appropriate. The active substance, cimicoxib, is of synthetic origin. No materials of human or animal origin are used in the manufacture of povidone, crospovidone, sodium laurilsulfate, macrogol 400 and sodium stearyl fumarate. The lactose is sourced from milk from healthy animals

under the same conditions as for human consumption, and is prepared without the use of any other ruminant materials other than milk and calf rennet.

The liver powder is sourced from pork livers. As regards BSE/TSE risks, pigs are not considered a risk animal and so the requirements of the TSE Directive 2003/63/EC and the Note for Guidance on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01) are satisfied.

Control tests during production

All the in-process controls during manufacture of the granules, tabletting and packaging, are well defined and have been justified.

Control tests on the finished product

Adequate specifications and routine tests suitable for this dosage form have been described to ensure the appropriate and consistent quality of the finished product. The tests include appearance and dimensions, average weight, uniformity of mass, uniformity of dosage units of half tablets, dissolution, assay, impurities and microbiological quality (according to the Ph. Eur. monograph 5.1.4.). Disintegration is tested as an in-process control. The identity of cimicoxib is verified by two independent tests (HPLC retention time and UV diode array analysis). The proposed specifications are in line with VICH guidelines and are justified by batch analysis and stability data. The dissolution test and conditions have been justified, and the limits applied have been based on the results from clinical batches. The proposed shelf-life specifications for the product are the same as the release specifications with one justified exception.

All analytical methods have been suitably validated, where applicable. Batch results of pilot scale batches, which comply with the specification, have been presented. The data include the clinical batches.

Stability

Stability studies (according to VICH guidelines) have been initiated on batches of all tablet strengths and then stored at both accelerated (40°C/75% RH) and long term (25°C/60% RH) conditions. The 6 month accelerated studies have been completed and up to 24 months data are reported from the long term studies. All results from these primary stability batches are well within the proposed specifications at both storage conditions. No significant change is observed in the cimicoxib assay for up to 24 months of long term storage, and the amount of impurities never exceeded 0.1%. Stressed studies have also been performed and the analytical methods for assay and related substances have been proven to be stability indicating. The stability data provided support a shelf-life for all strengths of the tablets of 3 years with no special storage precautions. An in-use study of half tablets has also been performed which covers two days in blister and 90 days (ongoing 49 days data available) in the tablet container.

Overall conclusions on quality

The active substance, cimicoxib, has been satisfactorily characterised and its synthetic process well described. Controls during manufacture are acceptable. The active substance is tested according to

satisfactory specifications and the methods used have been appropriately validated. Cimicoxib can be considered as a stable substance. Suitable stability studies according to VICH guidelines have been carried out on the active substance which support the proposed retest period of 3 years.

The finished product is presented as three strengths (8, 30 and 80 mg) of tablets. The rationale for the choice of the formulation is acceptable. The tablets are manufactured by a validated standard tablet manufacturing process comprising of wet granulation (common granulate for the three strengths), mixing and tabletting.

The excipients used are commonly employed in such tablet formulations and are acceptable, as are the packaging materials. All excipients contained in the tablets, except the flavouring agent (pig liver powder), are of pharmacopoeial grade quality. The microbiological and virological safety of the pig liver powder flavour have been substantiated. There are no concerns in relation to TSE with any of the ingredients of the product.

The finished product is tested according to acceptable specifications, and the analytical methods used in the control of the product have been satisfactorily validated. The critical quality attribute for adequate product performance is the particle size of the drug substance. A micronized quality of cimicoxib is therefore used in the drug product to ensure the necessary bioavailability and the particle size of the drug substance to be used in the manufacture is appropriately controlled. Suitable stability studies according to VICH guidelines have been carried out and these support the proposed shelf-life of 3 years. No special storage precautions are considered necessary.

The quality data and documentation provided are in accordance with the relevant VICH and EU guidelines.

3. Safety assessment

Pharmacodynamics

See section 4.

Pharmacokinetics

Three pharmacokinetic studies have been performed in rats *in vitro* and *in vivo*. Two GLP-compliant studies with ^{14}C-labelled cimicoxib, at a dose of 1 mg/kg bodyweight (bw) as a single administration, were performed to study the absorption, distribution, excretion and *in vivo* metabolism. The *in vitro* metabolism was studied in rat, dog, monkey and human hepatocytes. The results showed that cimicoxib is rapidly absorbed after oral administration (T_{max} = 1 hour) and widely distributed throughout the body. The bioavailability was high. Two main metabolites were observed, a demethylated metabolite and the glucuronide of demethylated cimicoxib. Cimicoxib was eliminated mainly via the faeces following biliary excretion, and the half-life in plasma was relatively short, approximately 3-6 hours. The pharmacokinetic profile in rats was similar to that in the target species, dogs.

For assessment of the user safety it is useful to compare the pharmacokinetic profiles in humans and rats. An *in vitro* study of the metabolism in hepatocytes showed similarities in metabolic

pathways. There were also some data in the human phase I clinical trial that showed that cimicoxib was rapidly, but incompletely, absorbed and that excretion was mainly in the urine.

Toxicological studies

Single dose toxicity

GLP-compliant oral single dose studies were conducted in rats and mice, and the results of these indicated a low acute toxicity potential.

Repeat dose toxicity

Repeated dose toxicity was studied in rats and dogs. No 90-day study has been performed according to the VICH guideline. However, two shorter and two longer studies, all GLP-compliant, in rats and dogs were provided. In rats, two studies were performed: the first was a 28-day study with a 14-day recovery period; and the second a 26-week study with a 6-week recovery period. In the target species, dogs, a 5-week study with a 14-day recovery period, and a 39-week study with an 8-week recovery period, were performed. In general the effects seen were typical for COX-2 inhibitors. The most prominent effects were seen on the gastro-intestinal tract with observed clinical signs such as diarrhoea, blood in the faeces, a hunched back, decreased motor activity, and a swollen and hard abdomen. At necropsy, gastrointestinal adhesions, ulcers of the small intestines and peritonitis were found. Changes in the relative weights of the kidneys, liver and adrenal glands were found, but only in the 28-day rat study. Lowering of the haematocrit and haemoglobin values was also observed. The effects appeared to be reversible in the cases where the animals did not die. NOEL values for the dog were determined to be 5 mg/kg and 1.5 mg/kg in the 5-week and 39-week studies respectively.

Tolerance in the target species

Target animal tolerance data are summarised in section 4 (Efficacy) of this document.

Reproductive toxicity

A GLP-compliant study of fertility and early embryonic development was performed in rats following dietary exposure to cimicoxib. As in other toxicity studies, the gastrointestinal tract was the main target with gastrointestinal disturbances and deaths with perforated ulcers at necropsy. The NOEL was set to 8 mg/kg/day. For male fertility, a NOEL of 100 mg/kg/day could be set (the highest dose tested), however no NOEL could be set for female fertility as effects were seen at all doses of cimicoxib with increases in the percentage of resorptions, pre- and post implantation losses, and a decrease in the number of live foetuses. No generational reproductive study was performed; however this can be accepted for use in a non food-producing species.

Studies on developmental toxicity were performed in both rats and rabbits. Preliminary studies were conducted to determine the dose levels to be used in the main studies. The maternal effects were, as expected, gastrointestinal alteration and in some cases, deaths. In rats, the foetal NOEL was 250 mg/kg/day (the highest dose tested in the main study), while the maternal NOEL was 50 mg/kg/day. In rabbits, a very high degree of post-implantation losses were seen in the dose finding study at doses above 60 mg/kg/day. A decrease in the percentage of live foetuses, and an increase in resorptions and post-implantation losses were seen in the main study. Malformations were seen at all doses and no foetal NOEL could be set. The maternal NOEL was set to 20 mg/kg/day. Since there are no data in pregnant bitches, the use of cimicoxib in breeding,

pregnant or lactating bitches is contraindicated and appropriate wording is included in the SPC (and package leaflet) accordingly.

Mutagenicity / genotoxicity

The genotoxic potential of cimicoxib was evaluated in a standard battery of GLP-compliant *in vitro* and *in vivo* tests. Cimicoxib did not induce mutations or chromosome aberrations *in vitro* and was also negative in an *in vivo* micronucleus test. According to the studies performed, cimicoxib is not genotoxic.

Carcinogenicity

No carcinogenicity studies were performed. Cimicoxib is not genotoxic, no structural alerts have been identified, and there was no signal indicating carcinogenic potential in the repeated dose toxicity studies. Consequently, the lack of carcinogenicity studies is accepted.

Studies of other effects

A GLP-compliant study on dermal irritation in rabbits showed that cimicoxib was slightly irritant, but not irritant enough to fulfil the criteria for classification as irritating to the skin.

The skin sensitisation potential was studied in a GLP-compliant study in guinea pigs (according to Magnusson and Kligman), the results from which led the Committee to conclude that cimicoxib should be classified as sensitising to the skin.

Special studies

Special studies were submitted for effects on the gastro-intestinal tract, the cardiovascular system and on renal function. The results of which are described in section 4.

Human observations

In a GCP-compliant Phase I clinical trial, cimicoxib was tested in humans in a double-blind randomized, placebo and active treatment-controlled study with the administration of single doses of up to 600 mg. The results showed that cimicoxib was well tolerated as a single dose. This information is useful in the assessment of the user safety of the product. The study also investigated some pharmacokinetic parameters.

User safety

A user safety assessment was provided with exposure scenarios for the veterinarian, the pet owner and children. For the veterinarian and pet owner, the cutaneous exposure when administering the tablet to the dog, and the oral exposure after hand-to-mouth transfer were calculated. However, because of the type of formulation of the product, that is, (compressed) tablets, these exposure scenarios are considered less relevant and the Committee concluded that no warnings were necessary regarding use of the product by pregnant women.

However, as cimicoxib may cause skin sensitisation, a user safety warning regarding the need to wash hands after use is included in the SPC (and package leaflet).

For children, accidental ingestion is the relevant exposure scenario, and this is likely to be only a single exposure. Calculation of the possible oral exposure of children is based on the ingestion of one tablet of the highest strength (80 mg) by a child weighing 10 kg, leading to a dose of 8 mg/kg. A human study shows that cimicoxib is well tolerated at a single dose of 600 mg in adults (approximately 8.33 mg/kg). Acute studies in rats also showed low acute toxicity. The product should therefore be kept out of reach of children, and the SPC, labelling and package leaflet carry appropriate warnings to that effect.

Environmental risk assessment

The potential environmental impact of cimicoxib was assessed in line with VICH guideline GL6, and as cimicoxib is intended for use in companion animals only, the assessment ceases at Phase I and no further environmental impact assessment is therefore necessary.

Overall conclusions on the safety documentation

Cimicoxib has a low acute toxicity potential.

In the repeated dose toxicity studies, clinical signs of gastro-intestinal disturbances were seen, and at necropsy gastro-intestinal adhesions, ulcers of the small intestines and peritonitis were found. These are predictable effects for any substances in the coxib-group. The effects seem to be reversible in animals which survived.

In the reproductive studies, effects on fertility were seen with increases in resorptions, pre- and post implantation losses and a decrease in the number of live foetuses. Malformations were seen at all doses in rabbits.

Cimicoxib is not genotoxic.

The user safety profile is considered acceptable with the appropriate user safety warnings in the SPC and package leaflet.

There is no risk for the environment.

4. Efficacy assessment

Pharmacokinetics

Information on the pharmacokinetics of cimicoxib in dogs is derived from one mass-balance study, one bioavailability study, one PK-PD study, one repeat dose PK study, one PK study in renal impaired, and from PK samples in a tolerance study. All studies were performed in Beagle dogs. Additionally, there is one comparative bioavailability study in different dog breeds.

Cimicoxib in the final formulation has a bioavailability of approximately 45%. Food affects the rate slightly, but does not affect the extent of its absorption. Cimicoxib is eliminated mainly through metabolism and excreted in the faeces (approximately 70%) with approximately 15% being excreted via the urine. Although the enzymes involved have not been fully investigated, CYP2C19

and CYP2D6 appear to be the major enzymes involved. Half-lives were around 2.5 - 4 hours, but up to 8 hours in Beagle dogs with a slow metabolism. Plasma exposure and peak concentrations seem to increase less than proportional, but no time dependency was seen. In the PK-PD study, it was evident that there were two Beagle populations with different elimination patterns. It was agreed to be most likely due to polymorphism of one or both of metabolising enzymes, based on the known polymorphism of the enzymes CYP2D6 and CYP2C19 in humans. The metabolism has not been fully investigated and there are subgroups of dogs where a slower metabolism may be observed. However, in the four other breeds investigated (Anglo-French Hounds, Pointers, Cavalier King Charles Spaniels and Bernese Mountain Dogs) no prolonged elimination half-lives were observed.

Based on a PK-PD study, EC_{50} and IC_{50} values were calculated for different pharmacodynamic endpoints and then simulated response-concentrations relationships for other doses (up to 8 mg/kg). The values varied between 216 and 452 ng/ml for different parameters. Based on the PK/PD study, a 2 mg/kg dose was chosen by the applicant for evaluation in the efficacy studies. Ten hours after administration of the final formulation, the concentrations are above a level of 100 ng/ml in six out of ten animals. At 24 hours, the concentrations are lower than the stated EC_{50}/IC_{50} values in all animals. Following a request to calculate the half-life and duration of response for each of the different pharmacodynamic parameters, the Committee concluded that considering the estimated differences in bioavailability and correcting for non linear PK it appears that the effect obtained with administration of the recommended dose of the final formulation is not maximal (about 75% of the maximal effect intensity is attained) and that overall no significant effect persists for the full 24 hours after dosing. Therefore the CVMP agreed the following sentence to be included in the SPC (section 5.1) and package leaflet: "In an *in vivo* inflammatory acute pain model, it was shown that the simulated effect of cimicoxib lasted for approximately 10-14 hours.".

Pharmacodynamics

The pharmacodynamic characteristics of cimicoxib are outlined from the results of 7 studies.

COX-1/COX-2 selectivity was explored in a study on two different human cell lines expressing only COX-1 or COX-2, and IC_{50} concentrations were determined. Selectivity for COX-2 was demonstrated and this characteristic was further confirmed in an *ex vivo* study, where the potential for COX-1 and COX-2 inhibition was determined in blood from dogs administered cimicoxib at a dose of somewhat less than 1 mg/kg bw. In this study, COX-2 inhibition at a maximum plasma concentration (377 ng/ml) was 86%, whereas it was only 27% for COX-1 inhibition. Selectivity corresponded quite well with the comparator, rofecoxib, although this is not authorised in use for dogs. Furthermore, the validity of the comparison is questionable because no PK profile was established for rofecoxib.

The potential for reducing inflammation, oedema and pain was explored in five experimental studies in rats. An anti-inflammatory effect was demonstrated in one single dose study and the ED_{50}, 0.2±0.04 mg/kg bw was established. In another single dose study using paw oedema, a much higher dose was needed to reach the ED_{25} (2.53±0.5 mg/kg bw). A 4 week study on induced arthritis demonstrated reduced cartilage destruction and a considerable reduction in paw swelling at a dose of 1 mg/kg bw, and the ED_{50} in this model was 0.18±0.01mg/kg bw. Cimicoxib treatment reduced hyperalgesia in a carrageenan model, and the ED_{50} was in that study was 0.23±0.03mg/kg bw. By contrast, no analgesic effect was noted in a tail-flick test where rats received single doses of up to 1000 mg/kg.

To conclude, cimicoxib is demonstrated to be selective for COX-2 inhibition in dogs, and studies in rats suggest anti-inflammatory and analgesic properties. The ED_{50} in rats was in most studies approximately 0.2 mg/kg bw.

In addition to the more general pharmacological data, the applicant provided 8 studies performed in rats and dogs to explore secondary pharmacological effects on: the GI tract; the cardiovascular system; and on renal function. With regard to effects on the GI tract, these studies further suggested that COX-1 inhibition is very limited and, furthermore, the generally less damaging effect of COX-2 specific substances, as compared to less selective NSAIDs, were demonstrated. One dog which received 30 mg/kg cimicoxib died, apparently due to cardiovascular effects, and *in vitro* data indicated cimicoxib related effects on dog Purkinje fibre function. Due to these findings, and the fact that adverse events related to cardiac function were noted in two dogs in the clinical studies, further information was requested on the potential cardiotoxic properties of cimicoxib. It was subsequently clarified and established that the death of the 1 dog was apparently related to surgical or anaesthetic complications, and the effects on Purkinje fibres were noted only at concentrations corresponding to more than 20 times the recommended dose of cimicoxib. Furthermore, no cardiovascular events were noted in the 26 week tolerance study. Finally, detailed information regarding the two cardiovascular events in the clinical studies suggested that a relationship to treatment was unlikely. From this additional information the Committee concluded that cimicoxib is associated with a low risk for cardiovascular adverse events.

In addition, two other studies in rats investigating the potential for adverse effects of cimicoxib administration on renal function and bleeding time indicated no adverse effects.

Target Animal Tolerance

Tolerance in the target species was investigated in a long term (26 week) tolerance study performed in healthy Beagle dogs, and in the safety data collected from the two clinical field studies performed to support the proposed indications. Additional information regarding tolerance is available from one 5 week and one 39 week toxicity study with a follow-up period in Beagle dogs (see section 3).

The 26 week GCP target animal tolerance study included 32 Beagle dogs divided into 4 equally sized dose groups, which received 0X, 1X, 3X and 5X recommended dose (2mg/kg bw). The results demonstrated (typically for an NSAID) that the target organ for toxicity is the gastrointestinal tract, and to a lesser extent, the kidneys. Diarrhoea was noted in 6 out of 8 dogs in the 3x group, and in all dogs in the 5x dose group. In addition, occult blood was noted occasionally in the faeces in these two dose groups. Gastrointestinal bleeding/inflammation was indicated by a decrease in haematology parameters and an increase in white cell count and fibrinogen in the same dose groups. Gastrointestinal insults were evident at necropsy as scattered areas with erosions/ulceration/haemorrhage of a slight to moderate magnitude, in different parts of the small and large intestines. A dose-effect relationship was indicated for GI effects, but in the 1X dose group no differences were noted from the control group.

A dose-related increase in renal effects was also noted. The main finding was papillary necrosis, of a minimal to slight magnitude, which affected 1 dog in the 1X dose group, 3 dogs in the 3X dose group and 6 dogs in the 5X dose group. No significant changes in blood urea, nitrogen or creatinine were noted during the study, suggesting the effects were limited from a clinical perspective. Apart from these findings, some deviances in other clinical pathology parameters were noted, but no deaths were recorded.

In the 5 week toxicity study, where Beagle dogs were treated with 1X, 2.5X and 6.5X the recommended dose for 5 weeks, the safety profile evident in the 26 week long term study was generally confirmed, although signs of renal affection were absent in the shorter study. From this study, the NOEL was determined to be 5 mg/kg bw (2.5X the recommended dose). A similar pattern was noted in the 39 week toxicity study were Beagle dogs were given 0.75X, 2X and 5X the recommended dose. However in the latter study, treatment related adverse events were clearly noted also at 2X the recommended dose, suggesting a very narrow safety margin. However it was clarified that exposure was substantially higher in this study (up to 5.8 times higher compared to the final formulation), due to the fact that a test formulation had been used. The Committee agreed this explained why the tolerance appeared worse in the 39 week study compared to the pivotal 26 week tolerance study. In both the 5 week and 39 week studies, no deaths and no signs of cardiac effects were recorded, and the clinical signs noted appeared to resolve during the follow-up period.

To conclude on the tolerance studies: a dose-related increase in effects of cimicoxib on the GI tract and kidneys was demonstrated, in line with what could be expected for any NSAID. At the recommended dose level however either no change, or only minimal changes to these organs were noted, suggesting acceptable tolerance. The risk for cardiovascular adverse events was demonstrated to be very low. One of the clinical studies appeared to indicate that gastrointestinal adverse events are more frequent during long term use of the product compared to the reference product. However, the higher incidence is mainly attributed to vomiting, which resolves after the cessation of treatment. The risk for serious adverse events is comparable to other NSAIDS. The SPC and package leaflet include appropriate information on risk mitigation measures. The Committee agreed that the tolerance can be regarded as acceptable for cimicoxib.

A palatability study in healthy Beagle dogs demonstrated that Cimalgex tablets exhibited a high acceptance rate (about 100%) when offered to healthy Beagle dogs. The Committee debated to what extent this result would correspond to acceptance in animals recently subjected to surgery or suffering chronic musculoskeletal pain, but as that cannot be predicted section 4.9 of the SPC (and the package leaflet) include the following information: "The tablets are flavoured and studies (in healthy Beagle dogs) show they are likely to be taken voluntarily by most dogs."

Dose determination / justification

To define an appropriate dose to be tested in a clinical setting, a PK/PD study in Beagle dogs was performed, in which an inflammation model was used with a placebo/test treatment cross-over design study. Kaolin was injected into a limb to induce inflammation, followed by a single oral dose of either placebo or cimicoxib. The administered cimicoxib dose was 20 mg per dog, corresponding to about 2 mg/kg bw. The bioavailability of this formulation was considerably higher than that of the final formulation to be marketed. The dogs were administered cimicoxib or placebo about 24 hours after the kaolin injection. The cimicoxib blood concentration was determined repeatedly before and during the first 48 hours after treatment, and clinical data [rectal temperature, skin temperature in the sole of the foot, foot circumference, crawling time through a tunnel, vertical force of the foot, lameness score, tolerance to heat-induced pain (withdrawal time)] was recorded before challenge, before treatment, and during the first 24 hours after treatment.

Two subpopulations were identified with regard to the speed of elimination ["slow" (n=4, mean half life 8.0 hours) and "fast" (n=8, mean half life 2.9 hours)]. It was noted that EC_{50} and IC_{50} values were considerably higher for the slow eliminators than the fast eliminators, which suggested that differences between these two groups is not only related to kinetics but also to pharmacodynamics.

However, no reasonable explanation to this phenomenon could be provided and it was concluded that the finding was an artefact related to the study design (only a few slow metabolisers).

PK/PD simulations were made for the dosing interval of 0.1 to 8 mg/kg bw, including four of the clinical parameters (rectal temperature, crawling time, vertical force of the foot and lameness score). The four parameters used in these simulations reflect the antipyretic and analgesic effects of treatment, whereas the anti-inflammatory effect is assessed more indirectly. From the assessment of effects on paw swelling, it appears that the anti-inflammatory effect is somewhat limited.

From these simulations it was concluded that the maximum effect is reached at doses of 1, 2, 3 and 1.5 mg/kg bw for the four different clinical parameters. Furthermore, doses above 2 mg/kg did not seem to increase the magnitude of the effect, but only prolonged its duration. However, the relevance of the simulation was questioned, as the pharmacokinetics of the substance is not linear and the relative bioavailability between the test formulation and the final formulation to be marketed was not investigated, but it was concluded that 2 mg/kg of this formulation corresponds to up to a two-fold dose of the final formulation. Considering the severity of the model, a target range was set at 100-200 ng/ml and compared with the plasma levels obtained in the repeat dose pharmacokinetic study (where Beagle dogs received 2 mg/kg of the final formulation). All the dogs reached the target range (100-200ng/ml) and this level was maintained for 10 hours after administration.

However, the target range calculations presented were based only on fast eliminators since the slow eliminators, for which EC_{50}/IC_{50} concentrations were about twice as high, were regarded as a rare phenotype which was unlikely to occur in the target population. Since the difference in EC_{50}/IC_{50} noted for these two sub-groups appeared to be an artefact, and not a physiological phenomenon, it was not considered obvious by the Committee that this subgroup could be excluded from the calculations. If the EC_{50}/IC_{50} calculations were based on the whole group of dogs, the target range for obtaining 50% of maximum effect would be about 200-400 ng/ml, confirming the uncertainties connected to the dose-finding concept.

This strategy for establishing a dose was considered in depth by the Committee. It is not evident that EC_{50}/IC_{50} concentrations are relevant for defining sufficient effect. Thus, the target range 100-200 ng/ml was considered uncertain and likely to be underestimated. Finally, the claimed 24 hour duration of effect is not supported by these data. Efficacy declined rapidly after 10-15 hours in the PK/PD study, although exposure was considerably higher in this study as compared to studies where the final formulation was used.

The Committee initially had some concerns relating to the facts that, firstly, according to the PK/PD study the duration of effect did not appear to correspond with the proposed 24 hours dosing interval, and secondly, that the proposed dose appeared to be in the lower part of the therapeutic window, and that these might result in insufficient pain relief in cases of severe pain. In response to these concerns the applicant provided simulations of the duration of effect which took into account the non-linear pharmacokinetics and the lower bioavailability of the final (marketed) formulation. From this, it was concluded that the duration of effect is somewhat shorter than 24 hours. Appropriate information is therefore included in both the SPC and package leaflet accordingly.

On the basis of the information provided from all the clinical studies, the Committee also concluded that treatment with the product is also efficacious for dogs with severe pain, not only for dogs with just mild and moderate pain. The claim in the product information is therefore justified.

Dose confirmation

No dose confirmation study was conducted.

Field trials

Peri-operative pain due to orthopaedic or soft tissue surgery

A multi-centre, randomised and blinded, non-inferiority study was performed in several EU Member States comparing the pain relieving effect of cimicoxib with a carprofen-containing product authorised for the treatment of post-operative pain. Client owned dogs that were candidates for either soft tissue surgery (e.g., castration, tumour excision, mammectomy) or orthopaedic surgery (e.g., fractures, ligament or joint dysfunction) were randomly allocated into the two strata: soft tissue surgery and orthopaedic surgery, to either cimicoxib or carprofen treatment.

All the dogs were 4 months or older, otherwise healthy according to clinical examinations, and had not received anti-inflammatory treatment close to the surgery. In both groups, treatment was initiated 2 hours before surgery. Treatment continued for 5 days post surgery in the carprofen group, and for 2-6 days post surgery in the cimicoxib group. In the latter group, treatment could be terminated if no sign of pain was noted at day 3. In the cimicoxib group, the dogs were dosed once a day with cimicoxib tablets at the recommended dose (2 mg/kg bw) throughout the study period, whereas in the carprofen group, treatment was initiated with parenteral administration (4 mg/kg bw) and then continued by the oral administration of carprofen at the same dose (4 mg/kg bw) throughout the follow-up period.

For the non-inferiority analyses, two different primary efficacy criteria where assessed. One was the assessment of pain during the first 24 hours using an established composite score (Association Véterinaire pour l'Anesthésie et l'Analgésie Animales (4AVet) pain scoring grid). Pain was assessed by use of this tool, before surgery and then 1, 4, 12 and 24 hours after surgery. The AUC for this period was compared between the two treatment groups. The other primary efficacy criterion was the proportion of responders to treatment at the end of follow-up. A responder was defined as a dog, which according to the investigator had at least acceptable analgesia.

In addition, different secondary endpoints were assessed by the investigator or the owner, such as the visual-analogue scale (VAS) scoring of pain, and also the assessment of pain related behavioural and physiological changes.

Non-inferiority tests were made on the intention to treat (ITT) and per protocol (PP) populations, based on the two primary efficacy endpoints and a 20% difference was pre-set as the inferiority limit. A large number of dogs (of which almost equal numbers were in the cimicoxib and carprofen groups) were withdrawn from the PP analysis, mainly due to the non-adherence of the protocol with respect to other treatments, especially at day 3.

Regarding the analgesic effect during the first 24 hours post surgery, non-inferiority was indicated for cimicoxib in comparison to carprofen on the basis of calculations made on log transformed ITT data. Non-inferiority was indicated for the entire population (point estimate 0.89, upper limit of the confidence interval (CI) 1.032) and also for the orthopaedic surgery group (point estimate for difference 0.84, upper limit of the CI 0.99). For the soft tissue group however, non-inferiority was not demonstrated (point estimate for difference 1.01, upper limit of the CI 1.31). However, when re-calculations were made on the latter group using non-transformed data, the hypothesis of inferiority could be rejected.

Regarding the proportion of responders at the end of follow-up for the ITT population, non-inferiority was also indicated (success rate: cimicoxib 100%, carprofen group 97.6%, difference 2.4%, lower bound of the CI -1.5%, non-inferiority limit -20%). Due to the high success rate, corresponding calculations could not be performed separately for the subgroups for soft tissue surgery and orthopaedic surgery.

For the PP population, non-inferiority regarding the analgesic effect during the first 24 hours of treatment was also indicated for the entire population (AUC mean: cimicoxib 4.41(±0.85) µg•hr/ml, carprofen 4.51(±1.14) µg•hr/ml, point estimate 0.90, upper limit of CI interval 1.164). Similarly, regarding the proportion of responders at the end of the study, non-inferiority was indicated for the PP population (success rate: cimicoxib 100%, carprofen 97.7%, difference 2.3%, lower limit of CI interval -5.2%). Due to the high withdrawal rate, no sub-group analyses could be performed on the PP sample.

A complementary analysis was made regarding the effect during the first 24 hours due to the fact that baseline VAS score indicated more severe pain in the carprofen group. Non-inferiority was tested for the two primary endpoints, excluding cases with 4AVet score > 10 (ITT) or > 8 (PP) at baseline. Non-inferiority was confirmed for the entire population and the orthopaedic surgery group, whereas data for the soft tissue surgery group was not presented,. However, based on the additional information provided, it was concluded that the efficacy of cimicoxib tablets for the management of peri-operative pain after soft tissue surgery had also been demonstrated. For the secondary efficacy endpoints no difference between treatment groups was noted.

Conclusions on efficacy for the peri-operative claim: The data provided support the proposed claim for the management of peri-operative pain resulting from orthopaedic and soft tissue surgery. Although some issues regarding the sensitivity of the two primary endpoints were initially unclear, further clarification was provided which confirmed the appropriateness of the primary endpoint to indicate efficacy during the first 24 hours (4AVet pain scoring grid). The second primary endpoint, reflecting the overall response during the entire treatment period, was considered only to offer limited information, due to its lack of sensitivity. Nevertheless the efficacy of the product was regarded to have been adequately supported by the fact that the non-inferiority of cimicoxib tablets (Cimalgex) compared to the positive control (carprofen tablets) was demonstrated with the 4AVet pain scoring grid. It was also considered appropriate to continue treatment for up to the recommended treatment period, depending on the clinical response.

Relief of pain and inflammation associated with osteoarthritis

A multi-centre, randomised and blinded, non-inferiority study, was conducted in several EU Member States comparing cimicoxib with firocoxib for the relief of pain and inflammation associated with osteoarthritis, in order to investigate the efficacy for this indication. (The latter control is authorised in the EU for the same indication.)

Client owned dogs which had exhibited X-ray confirmed clinical signs of osteoarthritis for at least one month were randomly allocated to cimicoxib (2 mg/kg bw once daily) or firocoxib (5 mg/kg bw once daily) treatment for a 90 day study. The study included mainly older dogs (mean age 8.8 years in both groups) of differing breeds without any signs of other illnesses at the time of inclusion in the study.

The effect of treatment was evaluated by repeated assessments during the follow-up period, of different clinical signs associated with osteoarthritis. The primary efficacy criteria was the improvement from day 0 to day 90 as a composite variable constituted by a weighted assessment -

in scores from 0-3 of the following parameters: lameness, pain, locomotion and oedema. Lameness was given the main influence in this composite score (coefficient 2) whereas the other three parameters were given equal weights (coefficient 1). In addition, the change over time in the composite score and the change in different separate clinical parameters, in pain assessment (by the animal owners) and in overall treatment success (judged by the investigator) were used as secondary efficacy variables. The weighted overall score (primary endpoint) tended to be higher at inclusion in the cimicoxib group (8.3±1.9) as compared to the firocoxib group (7.7 ± 1.7), ($p = 0.08$), whereas other clinical parameters were comparable at baseline.

To evaluate efficacy, non inferiority with regard to the primary efficacy endpoint was tested for cimicoxib in comparison to firocoxib and the inferiority limit was set to 20%. In addition, statistical comparisons of the difference between the two groups were made for the secondary efficacy endpoints. According to the calculations presented, non-inferiority was demonstrated for cimicoxib regarding the primary endpoint. For the ITT sample, the mean improvement in the primary endpoint was 5.58 ± 3.25 for the cimicoxib group and 5.11 ± 2.94 for the firocoxib group, the lower equivalence limit was -1.02 and the lower limit of the CI around the difference -0.21. Non-inferiority was confirmed in the PP sample. The secondary efficacy variables generally improved continuously and significantly over time, and no significant difference between the two treatment groups was noted.

Conclusions on efficacy for the osteoarthritis claim: the data provided support similar efficacy, within pre-set limits for inferiority, for Cimalgex as for the comparator (which has an EU marketing authorisation for the treatment of pain and inflammation associated with osteoarthritis in dogs).

Clinical safety

In the clinical study concerning the efficacy and safety of cimicoxib for the treatment of peri-operative pain, dogs which were candidates for either soft tissue or orthopaedic surgery were included and the effect of cimicoxib, in comparison to carprofen, was explored. The study included dogs of different breeds aged between 5 months and 15.5 years old, which were otherwise clinically healthy. No treatment related deaths were noted. Treatment was stopped for one cimicoxib treated dog due to vomiting, and for one carprofen treated dog due to surgical bleeding. The incidence of adverse events during the 3-6 days-long treatment period was quite similar in the cimicoxib group (30.7% of the dogs showed at least one adverse event) and the carprofen group (30.9%). As expected for NSAIDs, the most common adverse events were of GI origin. Vomiting seemed to be more common in the cimicoxib group (14.9%) compared to the carprofen group (8.1%) but it was not significantly different. Diarrhoea occurred rarely in the cimicoxib group (2 events) and in the carprofen group (4 events). Blood in the faeces was noted in one dog in the cimicoxib group. Signs of renal effects were noted in only 1 or 2 animals in both groups and appeared not to be severe and did not require further treatment. Changes in haematology and clinical pathology parameters attributed to the surgical procedure were noted in both groups.

From these data the safety profile of the two products, containing carprofen and cimicoxib, appeared similar. However, it must be noted that the treatment duration differed for the two groups, being 6 days for all the carprofen treated animals and only 3 days for many of the cimicoxib treated animals.

In the clinical study concerning the efficacy and safety of cimicoxib for treatment of osteoarthritis, dogs were treated with either cimicoxib or firocoxib at their respective recommended doses. Mainly older dogs (mean age of about 9 years), which were otherwise reasonably healthy, were included.

Adverse events expected from treatment with any NSAID were seen in both groups. It appeared adverse events were somewhat more common (although not significantly different) in the cimicoxib group compared to in the firocoxib group, mainly due to higher vomiting incidence (48.6%) in this group compared to in the firocoxib group (24%) but a lower incidence of diarrhoea in the cimicoxib group (18.9% of the dogs vs. 28% respectively). However no statistical difference ($p = 0.11$) in the proportion of dogs with at least one adverse event was noted between the cimicoxib group (59.7%) and the firocoxib group (40.3%). One severe adverse event was noted in the cimicoxib group (perforating ulcer) but this was not related to the treatment but to a neoplastic affection. Signs of considerable GI affection were also noted in the firocoxib group as evidenced by three cases of haemorrhagic diarrhoea. Clinical signs related to the urinary tract appeared to be more common in the cimicoxib group but according to the clinical chemistry findings there were no data to suggest any more pronounced renal adverse effects for cimicoxib. Cimicoxib and firocoxib appeared to affect renal function to a similar and minor extent. The four deaths which occurred during the study were not related to treatment. To conclude, a similar safety profile for these two products – and typical for NSAIDs – was noted, although vomiting may occur somewhat more frequently in cimicoxib treated dogs.

Data were provided from an experimental study in dogs, in which renal impairment (Glomerular Filtration Rate (GFR) decreased by about 60%) had been induced. From the results of this study the applicant stated that dose adjustments would not be needed in dogs with renal impairment. However, the Committee considered the data further and concluded that such a broad generalisation could not be made from the limited study.

To conclude on the clinical safety, the target animal safety study demonstrated that cimicoxib has a similar safety profile to other NSAIDs, where the target organ for toxicity is the GI tract and the kidneys to some extent. Adverse events were quite common at 3X and 5X the recommended dose, whereas they were minimal at the recommended dose, suggesting reasonable tolerance in healthy young dogs. The two clinical efficacy and safety studies performed in mainly elderly dogs confirmed the safety pattern noted in the tolerance study. During peri- and postoperative treatment GI disturbances were noted at a similar extent in the cimicoxib group as for the comparator, carprofen. Renal effects appeared in few animals but was not profound. The fact that post-operative treatment with cimicoxib was of a shorter duration than carprofen makes comparisons difficult. During treatment of osteoarthritis, adverse events related to the GI tract were also dominating. The incidence seemed to be more frequent in the cimicoxib group as compared to the control product (firocoxib) but it was not statistically significant.

Some changes over time in clinical pathology biochemical parameters for renal, and to some extent for hepatic effects was noted, but changes in connection to clinical signs were rare in both groups. In the pharmacodynamic as well as the clinical studies, adverse effects regarding cardiovascular function were indicated. However, it was made clear that the signs were likely not to be treatment related, and adverse effects indicated in *in vitro* studies were only noted at very high concentrations. From this information it is concluded that treatment with cimicoxib is not related to an increased risk for cardiovascular toxicity. In response to concerns regarding the increased risk in renally impaired dogs, appropriate precautions are included in the product information

The safety data presented for cimicoxib suggests that, regarding short term use (perioperative pain) tolerance is comparable to carprofen (already authorised in the EU for the proposed indications). Regarding long term use (osteoarthritis claim), no specific risk for adverse events as compared to firocoxib is suggested. However, the higher, but non-significant, incidence of adverse events is attributed to less severe events (vomiting) which resolve without cession of treatment (except in one case), whereas the risk for serious events appears similar to firocoxib. Compliance

with appropriate risk mitigation measures indicated in the product information could ensure adequate safety.

Overall conclusion on efficacy

The strategy used to establish the dose using PK/PD modelling was accepted although only one dose was investigated in the experimental dose finding trail and the final formulation was not used. This made the dose finding concept uncertain. However, the CVMP concluded that the dose was justified based on the fact that non-inferiority to the comparators had been demonstrated in the clinical field studies, and because the safety data demonstrated acceptable tolerance.

The applicant presented data, to support the proposed claim: *"for management of peri-operative pain due to orthopaedic and soft tissue surgery"*. With regard to the primary efficacy endpoint reflecting efficacy during the first 24 hours after surgery, non-inferiority to the comparator carprofen, was demonstrated. For the other primary endpoint reflecting the overall response, assessed at the end of the treatment period, the definition of the endpoint is vague and the assessment is in many cases based on quite scarce information on the dog's clinical condition during the treatment period. This endpoint was therefore not regarded as being sensitive and is therefore of limited value. Nevertheless, the data presented for the first 24 hours, where non-inferiority to the comparator was demonstrated, was considered by the Committee to demonstrate the claimed efficacy of the product over the recommended treatment period, taking into consideration the additional advice given on the product literature. The information presented enabled the Committee to further conclude that treatment with cimicoxib tablets is efficacious, independent of the magnitude of the pain, and that therefore no restriction on the severity of the pain was required.

The applicant also provided data to support a similar efficacy, within pre-set limits for inferiority, as the comparator firocoxib which is previously approved for treatment of *pain and inflammation associated with osteoarthritis.* The primary endpoint, reflecting improvement in lameness, pain, locomotion and oedema from day 0 to day 90 of the study, supported non-inferiority of cimicoxib in comparison to firocoxib.

Although PK/PD data indicated that the duration of effect is shorter than the proposed dosing interval, this is regarded as acceptable as appropriate information to this effect is included in the product literature.

The safety data presented for cimicoxib suggest that its tolerance is comparable to NSAIDs previously authorised for the proposed indications, apart from a slightly higher incidence of vomiting. Sufficient precautions and contraindications are included in the product information and bearing this is mind, the Committee concluded that the product's tolerance is regarded as acceptable.

5. Benefit Risk Assessment

Introduction

This is an application for the granting of a Community marketing authorisation for an NSAID, Cimalgex (cimicoxib) tablets for dogs, with the following indication: "For the treatment of pain and inflammation associated with osteoarthritis, and the management of peri-operative pain due to orthopaedic or soft tissue surgery, in dogs." The active substance is cimicoxib, a compound not previously authorised in veterinary medicine in the European Community. The application is supported by a full dossier.

Benefit assessment

Direct therapeutic benefit

Cimicoxib is a selective COX-2 inhibitor, which from a non-inferiority study is claimed to have a comparable effect as the previously authorised substance carprofen for the *management of peri-operative pain due to orthopaedic or soft tissue surgery*. Statistical evaluations demonstrated that the products are equally effective for the two types of surgery with regard to the reduction of signs of pain, assessed with use of an appropriate composite parameter, during the first 24 hours after surgery.

A similar effect with regard to the *relief of pain and inflammation associated with osteoarthritis* for cimicoxib as for the comparator substance (firocoxib) was demonstrated in another non-inferiority study. The reduction of clinical signs of disease, measured by a composite score containing signs of lameness, pain, locomotor disturbance and oedema, was similar within pre-set limits in the two treatment groups during a 90 day follow up study in dogs with confirmed chronic osteoarthritis.

Additional benefits

No additional benefits have been identified.

Risk assessment

The risks associated with Cimalgex treatment appear to be comparable to the two other NSAIDs (firocoxib and carprofen) which were used to explore its clinical safety.

Adverse events on the GI tract and to a lesser extent on renal function could be expected. Although the total incidence of such adverse events is comparable with these previously authorised products, vomiting appears to be a more frequent adverse event, but not statistically significant, in Cimalgex treated animals. From all the information provided, it can be concluded that treatment with cimicoxib is not connected to an increased risk of cardiovascular adverse events. The reproductive toxicity studies in the preclinical data show effects on fertility and foetal development that could pose a risk when used in breeding or pregnant dogs (bitches), and there are no data on lactating animals. A contraindication is therefore included in the SPC and package leaflet regarding use of the product in breeding, pregnant and lactating dogs.

Due to the tablet formulation there will be limited dermal exposure of the user. Since cimicoxib may cause skin sensitisation, a recommendation to wash hands after handling is included in both the SPC and package leaflet. Cimicoxib has a low toxic potential following acute oral exposure. Accidental ingestion of a tablet of the highest strength by a child weighing 10 kg would lead to a dose of 8 mg/kg. A human study shows that cimicoxib is well tolerated at a single dose of 600 mg in adults (approximately 8.33 mg/kg). The product should nevertheless be kept out of reach of children and the standard warnings to this effect are included in both the SPC and package leaflet.

Evaluation of the benefit risk balance

Based on the outcome of the clinical field studies, the efficacy has been supported for the claim "*management of peri-operative pain due to orthopaedic or soft tissue surgeries*". Furthermore, the efficacy has also been supported for the claim "*relief of pain and inflammation from osteoarthritis".*

Although the PK/PD data indicated that the duration of effect is shorter than the proposed dosing interval, the Committee regarded this as acceptable as adequate information had been included in the product information.

The data presented suggest that the safety profile of Cimalgex is similar to the other NSAIDs used as controls, and thus acceptable tolerance for the target species has been demonstrated. Appropriate and justified precautions and warnings are included in the SPC and package leaflet.

User safety can be assured by the appropriate precautionary measures in the product information (SPC and package leaflet).

The quality of the active substance and drug product is considered adequate.

Overall, the benefit risk balance is considered positive for Cimalgex 8 mg, 30 mg and 80 mg tablets for dogs.

Conclusion on benefit risk balance

The information provided in the dossier and in response to points raised was sufficient to confirm an overall positive benefit-risk balance for this veterinary medicinal product.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for Cimalgex 8 mg, 30 mg and 80 mg tablets for dogs was considered to be in accordance with the requirements of Directive 2001/82/EC as amended and that the benefit-risk balance was favourable.