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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report of an application for the granting of a community marketing authorisation for Recuvyra (EMEA/V/C/002239)

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

Summary of the dossier

Recuvyra is a non-aqueous transdermal solution containing as active substance fentanyl, an opioid analgesic.

It is presented in packs containing 1 vial (of 10 ml) along with 1 adaptor, 15 syringes and 15 applicator tips. Recuvyra is applied topically, 2-4 hours prior to surgery with a specially designed, novel applicator, and then absorbed through the skin.

The product is indicated for use in dogs for the control of post-operative pain associated with major orthopaedic and soft tissue surgery. Dogs of more than 20 kg bodyweight should remain at the veterinary clinic for 48 hours after application.

Part 2 - Quality

Composition

Recuvyra is a non-aqueous, transdermal solution containing 50 mg/ml of the active substance fentanyl dissolved in isopropyl alcohol. It also contains octyl salicylate 5% w/v. The product has been formulated as an unpreserved, non-aqueous, transdermal solution.

Container

The primary container is a Type I amber glass vial closed with a 20 mm grey butyl rubber stopper and aluminium overseal; each vial contains 10 ml of the solution.

The product is supplied with a dosing device consisting of a vial adaptor which enables a luer connection with the vial. Fifteen, 3 ml polypropylene syringes (luer connections), each with a silicone O-ring fitted to the plunger, are supplied with each vial and adaptor. Fifteen applicator tips are also provided in each pack. These have a twin-pronged shape with an orifice on each of the two tips, from where the solution is delivered, and these facilitate even distribution of product on either clipped or unclipped skin surfaces.

Development pharmaceutics

The formulation has been developed as a transdermal solution to be applied onto intact skin. It is a non-aqueous formulation consisting of the active substance, fentanyl, a co-solvent (octyl salicylate) and the main vehicle, a volatile solvent (isopropyl alcohol) which rapidly evaporates following application to the skin.

In the development pharmaceutics section, the applicant explained their aim of developing a proprietary transdermal delivery system (that they term a “patchless” transdermal delivery system). It is claimed that a single topical application of Recuvyra forms a depot of fentanyl within the dog’s skin which provides a continuous, long acting, systemic delivery of fentanyl for up to 4 days. Satisfactory evidence has been provided on how, following administration, the product does not easily run/wash off; thus ensuring that a concentration gradient is maintained and optimum active substance flux is achieved for up to 4 days.

With regard to administration of the product, the applicant has specified the 'residual volume' of the syringe applicator and how this is accounted for when administering a dose of the product. The applicant has successfully demonstrated the ability of the product to accurately deliver the required nominal dose using the syringe applicator. The applicant has also indicated the total area of skin to be treated by each of the 2 orifices of the applicator tips, for each of the dose volumes specified in the SPC. The relationship between the applied dose and the surface area treated has also been satisfactorily investigated.

The recommended dose is a single administration of 2.6 mg/kg bw, which corresponds to a dose range from 0.2 to 3.0 ml, depending on the dog's bodyweight.

Method of manufacture

Fentanyl and octyl salicylate are dissolved in the majority of the isopropyl alcohol, after which the remaining amount of isopropyl alcohol is added. The solution is then filtered and filled into the vials. The applicant has provided a commitment that the in-process testing will be defined as part of the production scale process validation. This is to be conducted on 3 commercial scale batches of the product. The applicant has updated the process validation protocol to include tests for related substances, microbial quality (in accordance with Ph. Eur. 5.1.4), extractable volume (in accordance with Ph. Eur. 2.9.17) and an assay for octyl salicylate, pre and post-filtration.

Control of starting materials

Active substance

The active substance, fentanyl, is described in a monograph in the European Pharmacopoeia (Ph. Eur.). Fentanyl active substance has been demonstrated to meet the requirements of the Ph. Eur. Monograph, and a valid EDQM Certificate of Suitability (CEP) has been provided. Additional tests are stated on the CEP.

A re-test period of 4 years, when stored below 25°C in amber glass bottles or polyethylene bags placed in high density polyethylene (HDPE) drums, is reported in the Certificate of Suitability.

Excipients

Isopropyl alcohol conforms to the Ph. Eur. monograph. It is used as a solvent in the formulation but also acts as an antimicrobial preservative.

The Ph. Eur. has no monograph for octyl salicylate. The octyl salicylate in this product conforms to a monograph in the US pharmacopoeia (USP), USP 31. It is used as a co-solvent within the formulation. Since the excipients comply with the pharmacopoeia monographs, no further information is required.

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

None of the starting materials used for the active substance, fentanyl, or for the excipients used in the finished product are risk materials as defined in Section 2 of the combined CPMP/CVMP "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (EMEA/410/01 Rev. 2).

Control tests during production

During manufacture, the following in-process controls are carried out: appearance; assays of fentanyl and fentanyl related substances; assay of octyl salicylate; specific gravity; microbial quality; fill volume; leak checks on empty vials; and, visual inspections of the secondary packaging. The acceptance criteria are found acceptable.

Control tests on the finished product

Descriptions of the methods used for the control of the finished product (clarity, colour, identity, average fill volume, assay, specific gravity, extractable volume, non-routine test for microbial quality) and the specifications were provided. The methods have been described in sufficient detail and the specifications proposed are appropriate to control the quality of the finished product and are justified.

The release specifications are appropriate to control the quality of the finished product. The same assay limits are used in the shelf-life specification. The absence of a test for related substances has been justified by the lack of detection of any such substances in the stability studies on the finished product. The results from three pilot scale batches demonstrate compliance with the specification.

The non-routine frequency of testing (on every 10th batch, and also at least one batch of product annually) for microbial quality has been justified.

Stability

Three pilot scale batches have been stored at 25°C/60% RH for 30 months, at 30°C/65% RH for 30 months and at 40°C/75% RH for 6 months, in the marketed packaging (amber glass vials). Little change in the physical characteristics of the solution was observed. The fentanyl content remained unchanged and no impurities were detected above the VICH reporting threshold (0.3%). The data provided support the proposed shelf-life of 3 years, with “no special precautions for storage”. The applicant has committed to place the first three commercial scale batches in a VICH stability study.

The results from a photostability study demonstrate the product is not affected by light in the marketed packaging (amber glass vials). The product has also been shown to be stable following freeze thaw studies.

In-use stability testing has been conducted on batches of the product stored for 17 months and 36 months, respectively. Based on the results of these studies the proposed 30 day in-use shelf-life (after first broaching the vial with the needleless adapter) is considered acceptable.

Overall conclusions on quality

The product is a simple non-aqueous transdermal solution for topical application on dogs. The administration device is novel and has been shown to be suitable for the intended use of the product.

The dossier provides appropriately detailed descriptions of the active substance and finished product, and demonstrates that production of the active substance and the product leads to consistent quality of this non-aqueous transdermal solution. The analytical methods are well described, and data of their validation confirm their suitability.

The retest period for the active substance is justified. Stability studies on the product have been performed which demonstrate that over the proposed shelf life no significant changes are observed to the physico-chemical properties. Based on the data provided, the proposed shelf-life of 3 years with no special precautions for storage is considered acceptable. The applicant has provided a commitment

that the first three commercial scale batches of product will be released according to the current version of the finished product specifications and placed onto stability under VICH conditions and tested to the current version of the shelf life specification.

Overall the documentation on quality relating to both the active substance as well as the final product is satisfactory and provides adequate assurances that a product of consistent quality will be produced.

Part 3 – Safety

Safety documentation

Pharmacodynamics

Fentanyl is a pure μ-opioid-receptor agonist considered to be 100 times more potent than morphine. In addition to its analgesic and sedative effects high doses of fentanyl in dogs result in decreased motor activity, ataxia, decreased responsiveness to auditory stimuli, bradycardia, respiratory depression, salivation, and defecation. These effects are linked to μ_2 receptor activation. Other effects of μ-opioid receptor agonists in dogs include vomiting by direct stimulation of the emetic centre, cough suppressant activity, hypothermia by lowering the temperature set-point, mild miosis, reduced urine production, inappetence and constipation through direct stimulation of μ- and δ-receptors in the gastrointestinal tract. In general, the sedative effects of fentanyl and other μ-opioid receptor agonists increase with dose.

Pharmacokinetics

Absorption:

Recuvyra is a volatile liquid solution. Following application of the product to the skin surface, fentanyl is rapidly absorbed and deposited in the *stratum corneum.* Following solvent evaporation and drying, approximately 2 - 5 minutes after application, fentanyl and octyl salicylate are absorbed into the *stratum corneum*. Fentanyl partitions from the *stratum corneum* through the deeper skin layers and into the systemic circulation, over a period of days. Due to the fact that the absorption phase from the *stratum corneum* into the plasma is long compared to fetanyl's relatively rapid elimination rate; Recuvyra exhibits "flip-flop" kinetics. The pharmacokinetic profile of Recuvyra is characterised by first-order absorption half-life being 74 hours in a clinical population of dogs and 117 hours in laboratory dogs. Plasma fentanyl concentrations typically peak 10 to 18 hours post administration.

Studies in beagle dogs revealed that a dose of 2.6 mg/kg bw (Recuvyra 1 ml/20 kg) administered onto the skin provides plasma concentrations above 1 ng/ml from about 6 until about 112 hours post administration. A higher dose (5.2 mg/kg) resulted in far higher concentrations and increased the duration above the 1 ng/ml level for 168 hours post dosing. A lower dose (1.3 mg/kg) maintained plasma concentrations above 1 ng/ml between 36 and 72 hours post dosing. Since the 5.2 mg/kg dose can lead to serious adverse drug reactions, the 2.6 mg/kg dose was considered as the most appropriate to provide therapeutic concentrations for the desired duration. Dose-linearity was shown in pharmacokinetic studies using similar transdermal fentanyl formulations.

Distribution:

Fentanyl distributes rapidly into a variety of tissues and readily crosses the blood-brain barrier. Following intravenous dosing, brain and cerebrospinal fluid fentanyl concentrations equilibrate with

plasma within 10-20 minutes. Fentanyl has a relatively large volume of distribution, approximately 10 l/kg in the dog. Fentanyl plasma protein binding is estimated to be approximately 60% in dogs.

Metabolism / Elimination:

In humans, fentanyl is primarily metabolised by the P450 3A4 isoenzyme system. The drug appears to be metabolised primarily by oxidative N-dealkylation to form norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Fentanyl is also metabolised extensively in the dog although the exact metabolic pathways are unknown. Urine collected for 6 hours in dogs contained 36% of all the ^{3}H-fentanyl radioactivity administered, but only 4% of the administered fentanyl was excreted as unchanged fentanyl. Excretion via faeces is only minor.

Fentanyl clearance ranges from 1.7 to 4.7 l/kg/h in dogs. The corresponding elimination half-life of intravenously administered fentanyl is short being 0.76 to 6.0 hours.

Toxicological studies

Single dose toxicity

When administered intravenously (as fentanyl citrate) LD_{50} values of 2.9 to 11.2 mg/kg have been reported in the rat. Pharmacological effects have been observed at far lower levels: 2.5 µg/kg in rats (analgesia and behavioural changes) and respiratory depression has been described at 20 µg/kg in rats. The lowest intravenous toxic dose in man is 2 µg/kg, inducing somnolence and respiratory depression. When given orally, slightly higher LD_{50} values were recorded in rats (18 mg/kg) and mice (368 mg/kg).

Data on the acute topical toxicity of fentanyl have been provided for dogs, and are reported below ("tolerance").

Repeat dose toxicity

No laboratory animal studies on the effect of repeat application have been provided.

However, the applicant has conducted two animal safety studies in dogs with repeat topical fentanyl dosing, as reported below ("tolerance").

Tolerance in the target species of animal

The tolerance of soluble fentanyl solution has been examined in a single dose toxicity study studying multiple doses of fentanyl; and three repeated dose toxicity studies.

Single dose

In the first study (019003), a single dose of the recommended therapeutic dose (RTD) of 2.6 mg fentanyl/kg bw, 7.8 (3X RTD) or 13 (5X RTD) mg fentanyl/kg bw was administered topically to six dogs per group. A fourth group included untreated (placebo) dogs.

A few incidences of sedation were seen in dogs treated at 2.6 mg/kg. Moderate to severe (dose related) sedation was seen in the 7.8 mg/kg-group and 13 mg/kg-group. Decreased food consumption and faecal output correlated well with the levels of sedation. Heart rate decreased in a dose-dependent manner over the first few days after administration. By Day 3, the heart rate of the treated was similar to untreated control animals, but for a few days thereafter many of the dogs that received the test

product had heart rates that were greater than the controls. Although variability in the respiratory rates was noted prior to treatment, it appeared that respiratory rate decreased in many of the animals in the highest dose groups.

Bodyweight decreased over the first week post application as the dogs were not eating or drinking while sedated. Although body weight increased in most animals during the second week post dose, most of the individual animals in the treated groups still weighed less than they did on Day 0.

In general, the values for haematology, coagulation and clinical chemistry parameters were within normal ranges. There was a reversible effect on the eye, with lens opacity seen for a period of 11 days post dose. This effect could be a result of corneal drying due to the extended sedation observed in the two highest dose groups, and an appropriate warning has been included in the SPC.

Repeated dose

2 weeks

In the repeated dose study, 4 male and 4 female purpose-bred laboratory mongrel dogs received local applications of 0, 2.6 (1X RTD), 5.2 (2X) and 7.8 (3X) mg fentanyl/kg. Three applications were made 4 days apart on Days 0, 4 and 8.

Mean plasma fentanyl concentrations ranged from 1.42 to 4.08 ng/ml, 3.07 to 10.7 ng/ml and 3.33 to 25.6 ng/ml in dogs receiving 2.6 mg/kg (1X RTD), 5.2 mg/kg (2X) and 7.8 mg/kg (3X), respectively, indicating moderate accumulation of plasma fentanyl concentrations after administration of the topical fentanyl solution at 4-day intervals.

A slight sedation associated with a pharmacological opioid-response was observed in dogs dosed with 2.6 mg/kg of fentanyl topical solution every 4 days. At higher doses the sedation was worse with concomitant changes in food and water intake, loss of weight, decreased heart and respiratory rates and decreased body temperature. Fatal serious side-effects occurred in the two highest dose groups, due to renal failure secondary to hypotension produced by gastrointestinal hypomobility. Therefore, the dose of 2.6 mg/kg bw fentanyl topical solution, administered every four days, was considered to be safe. Nevertheless, overdosing and treatment prolongation after the first administration should be strictly avoided as a two-fold increase in the dosage may be lethal in dogs when repeated after 4 days.

16 weeks

In another study mongrel dogs received a topical fentanyl solution in the final formulation administered weekly for 16 weeks at doses of 0, 2.6 (1X), 5.2 (2X) and 7.8 (3X) mg fentanyl/kg. Dose-dependent sedation was transient for several days following each dose and no sedation was observed by the time the subsequent weekly dose was given. Tolerance to the sedative effects of fentanyl developed over time. Heart rate, respiratory rate and body temperature all decreased transiently following each administration of topical fentanyl solution but mean values returned to normal by the time the subsequent weekly dose was given. Statistically significant ($P < 0.05$) evidence was noted of tolerance to the hypothermic effects of topical fentanyl solution. Faecal abnormalities and decreased appetite were observed in all treatment groups. No changes in clinical pathology variables were detected but after 16 weeks of weekly fentanyl administration, minimal and reversible fentanyl treatment-related histological changes were noted in the liver and in the skin at the 5.2 mg/kg dose.

4 weeks

In another pilot tolerance study, repeated administration of Recuvyra was evaluated in Beagle dogs. Each dog received a topical dose every 4 (Group 1) or 7 (Groups 2 and 3) days for a total of 28 days. The dosage was 2.6 mg/kg in Groups 1 and 2, and 3.5 mg/kg in Group 3.

Mean food consumption was decreased for the first 2-3 weeks following the start of administrations with topical fentanyl solution, but thereafter returned to pre-treatment levels. Coincident with the period of decreased food consumption, mean body weight also dropped during the first 2-3 weeks of treatment. Rectal body temperature showed a close temporal relationship with plasma fentanyl concentrations. Sedation was very mild and variable.

Conclusion on target animal safety

In conclusion, the four tolerance studies show that Recuvyra even at the recommended dose of 2.6 mg fentanyl/kg bw causes mild transient adverse drug reactions including sedation, hypothermia, bradycardia, loss of appetite, loss of weight, diarrhoea and emesis. The reactions are related to the pharmacological effect of fentanyl on the μ-opioid receptors in CNS and gastrointestinal tract. At 5.2 mg/kg and higher doses the adverse events were serious. Appropriate warnings have been included in the SPC and product literature.

In addition, as Recuvyra is a long-acting opioid with a novel delivery mode, and clinical studies undertaken under GCP conditions might not reflect a "real life" situation, the applicant will provide an augmented pharmacovigilance reporting system in a representative number of dogs.

- Veterinarians will be surveyed to record their, and any owner reports or experiences. Data collected would include but not be limited to: number of dogs treated, indications, adverse reactions, anesthesia, other analgesics and concomitant medications used, clinical impressions. The results of these surveys will be compiled, analysed and submitted together with the 6 month PSUR report. Additionally, if any major or significant finding is reported in these surveys, the EMA would be notified immediately (within 72 hours).
- All PV investigations will be extremely thorough. Following the report of any adverse reactions, the owners and veterinarians will be contacted. Data collected will include the history of the case, reason for surgery, premedications, anesthetic regime, dose and timing of Recuvyra, observations in the clinic, other medications, description and timing of the adverse reactions, any interventions or reversals, and outcome will be compiled and documented.

Tolerance of Recuvyra is also reported in the field studies. See under Part 4.

Reproductive toxicity

Female Sprague-Dawley rats were administered fentanyl continuously using chronically implanted osmotic minipumps for 2 weeks before breeding and during the entire period of pregnancy. Fentanyl was administered at 10, 100, and 500 μg/kg/day. Reproductive indices were determined and the 1,046 offspring delivered at caesarean section were examined for external, visceral, and skeletal abnormalities. There were no reproductive abnormalities or teratogenic findings in any of the fentanyl-treated groups. Thus it may be concluded that fentanyl is devoid of adverse reproductive effects in Sprague Dawley rats up to doses of 500 μg/kg/day administered by osmotic minipumps.

In contrast, another study revealed that a dose of 1.25 mg/kg subcutaneously significantly decreased the pregnancy rate in rats. Further doses of 30 μg/kg (intravenously) or 160 μg/kg (subcutaneously) given for a period of 12 to 21 days have been reported impair fertility and to have an embryocidal effect with an increase in resorption in rats.

However, no data on reproduction were provided in the target animal. The CVMP therefore concluded that Recuvyra should not be used in pregnant or lactating bitches.

Mutagenicity / genotoxicity

A comprehensive battery of mutagenicity studies have been conducted with fentanyl as test substance.

An Ames test was performed using the 4 *Salmonella typhimurium* required (TA 1535, 1537, 98, 102) and *E. coli* wv2 uvrA in the presence and absence of S9 mix. The highest tested concentration was 5000 µg/plate. Negative results were obtained in all cases.

Chromosomal aberrations were evaluated *in vitro* using CHO cells with negative results in all cases.

In vivo potential activities of fentanyl were investigated in a mouse micronucleus assay where sublethal and lethal doses (up to 25 mg/kg) were given intraperitoneally. Fentanyl was not shown to possess any clastogenic properties in this study.

The CVMP concluded from the studies conducted that fentanyl and its metabolites are not mutagenic substances.

Carcinogenicity

As no mutagenic properties were identified, no further studies on carcinogenicity were provided, which is acceptable.

Studies of other effects

Skin irritation studies in rabbits showed that the product is irritating to skin. In the mouse local lymph node assay the product did not induce any delayed contact hypersensitivity or any local irritation. According to the OECD toxicity testing Recuvyra is classified as: irritant to skin and eye, not a sensitizer to skin, and not toxic via inhalation.

However, in the clinical studies, no effects on the skin were noted in the target species.

User safety

The product is intended for use in individual dogs and will only be administered by professional users in clinical settings. The users are advised to use latex or nitrile gloves, eye protection and suitable protective clothing when handling the product. In addition, the applicant has committed to only distribute the product to veterinarians trained in the use of the product. Appropriate training materials will be developed by the applicant.

The applicant has provided limited data on the toxicity profile of octyl salicylate and has amended the User Risk Assessment accordingly. As this excipient has been used in topical products for human use for many years with an acceptable safety record, the data provided are considered satisfactory.

Exposure of the user

Contamination of the user is possible by accidental spillage, if the equipment is leaking, or during cleaning.

Main exposure will likely be dermal contact, by handling the product or handling or stroking a treated dog. The published therapeutic range for fentanyl is 0.2 to 1.2 ng/ml. In a phase I study for a human product, it was demonstrated that 20.6 mg in a topical fentanyl solution resulted in a maximal plasma

concentration of 0.3 ng/ml, which is near the lower level of the therapeutic range in humans. Such a dose level can already be reached with the equivalent of a dose of Recuvyra for a small dog (6 kg bw). As small amounts of the product might lead to pharmacological effects in people, the user warnings and the professional training provided should address any risks associated with handling the liquid formulation.

Approximately 2% of the dose is recovered on the dog skin 24 after treatment. Taking a worst case scenario for the treatment of a single large dog weighing 70 kg, the user stroking the dog would potentially be exposed to 2 % of 4.0 ml of product (50 mg/ml) that means 4 mg fentanyl. As stated above, 20.6 mg in the topical fentanyl solution resulted in a maximal C_{max} of 0.3 ng/ml in adults, which is close to the lower level of the therapeutic range. It can then be deduced that it is unlikely that 4 mg (approximately 7 times less) gives plasma levels likely to result in adverse effects in adults. However, in children the dose and hence the potential for adverse effects is higher.

The risk to a child coming into contact with a treated animal is related to acute topical or oral exposure and is dependent on the time elapsed since application. The proposal to hospitalise all dogs ≥20 kg bw for 48 hours is intended to address these potential routes of exposure by a child. It is considered that this time frame for medium to large dogs provides reassurance with respect to the risks to the child.

Conclusion including the risk management proposals

As Recuvyra will only be administered by professional users, the overall risk of direct exposure to fentanyl during administration is low. To avoid accidental contact with skin or eyes personal protective equipment are mandatory when handling this product. Latex or nitrile gloves, eye protection and suitable protective clothing should be worn. These precautions are mentioned in the summary of product characteristics. In addition, the applicant will ensure that appropriate risk communication about the risks related to human exposure to the product is provided to veterinarians expected to use Recuvyra, by providing educational material to train veterinarians in the correct and safe use of the product.

For the majority of persons (e.g. animal owners), the risk of exposure after administration will be limited to dermal contact by stroking a treated dog at the side of administration. Exposure in this situation is markedly reduced by preventing contact with the dog within the first 72 hours after application of the product. The product information therefore includes detailed user warnings, and recommends for dogs of more than 20 kg bw to remain with the veterinarian (clinic) before a dog is returned to the owner's family and people, in particular children, or other household pets are allowed contact with the treated dog.

In addition, the product is presented with a novel delivery system, providing a childproof container which can only be used with specially designed syringes for single use.

The CVMP considered that the user safety warnings together with the design of the container plus delivery system as well as the commitment of the applicant to provide adequate training to the veterinarian on the correct use of the product, and risk mitigation measures in regard to user safety, satisfactorily address the potential routes of exposure to the professional user, to the pet owner and their family.

Environmental risk assessment

A Phase I ERA carried out in accordance with VICH guideline 6 was provided which showed that exposure of the environment was not extensive and the assessment of the impact on the environment ended at Phase I.

Overall conclusions on the safety documentation

Recuvyra contains fentanyl as the active substance, which is a specific and selective μ-agonist with morphinomimetic properties about 100 times more potent than morphine against pain. Fentanyl is suitable for topical administration because of its physiochemical properties (high lipophilicity and moderate molecular weight).

Data from human observations indicate a therapeutic window of plasma fentanyl in the range of 0.2-1.2 ng/ml. A fentanyl concentration in plasma of 1 ng/ml has been accepted to control pain in dogs; thus a dose of 2.6 mg/kg has been established to achieve plasma concentrations above 1 ng/ml for at least 4 days after administration.

Tolerance studies revealed that even at 2.6 mg/kg topical fentanyl solution causes transient adverse events in treated dogs, including sedation, hypothermia, bradycardia, loss of appetite, loss of weight, diarrhoea and emesis. At 5.2 mg/kg and higher doses the adverse events were serious.

Recuvyra does pose a serious risk for users. The product is to be used exclusively by professional users wearing personal protective equipment; however, there is a potential risk to the dog owner and their family (and other household pets) following contact with the application site up to 72 hours post-application. It is therefore recommended that treated dogs of more than 20 kg bw remain in the veterinary clinic for 48 hours following application of the product, and the applicant has committed to provide specific educational material to train veterinarians in the correct and safe use of the product.

The use of Recuvyra is not expected to pose a risk for the environment when used in accordance with the SPC.

Part 4 – Efficacy

Pharmacokinetics

See section 3

Pharmacodynamics

See section 3

Target Animal Tolerance

See section 3 and field studies below.

Dose determination / justification

No dose titrations studies have been conducted, but based on literature data and the PK-PD study (see part 2 / section pharmacokinetics); the applicant concludes that a threshold of 1 ng fentanyl /ml plasma has to be achieved to control pain. The results obtained after Recuvyra application to the skin showed that the 2.6 mg/kg dose maintained concentrations above 1 ng/ml from about 6 hours post-dosing (4 to 8 hours) until about 112 hours post-dosing (96 – 120 hours). A higher dose (5.2 mg/kg) resulted in far higher concentrations and increased the duration for which expected therapeutic concentrations were maintained. However, side effects are likely to occur at this dose. A lower dose (1.3 mg/kg) only maintained plasma concentrations above 1 ng/ml for a limited period with a late

onset of action (36 h post dosing with effects lasting only 36 hours). Thus the dose of 2.6 mg/kg dose is a compromise between duration of action and safety aspects.

Dose confirmation

No dose confirmation studies have been conducted.

Field trials

Two clinical trials performed in Europe are available. The first trial investigated the effects of Recuvyra in post-operative pain following orthopaedic surgery in dogs. In the second trial post-operative pain following soft tissue surgery was evaluated.

Orthopaedic surgery

In the orthopaedic surgery study (cruciate ligament surgery), 104 dogs received Recuvyra and 106 dogs received a reference product, containing buprenorphine. Recuvyra was administered topically as a single dose (2.6 mg/kg bw) about 4 hours prior to intubation. Buprenorphine was administered intramuscularly (20 µg/kg) 2-4 hours prior to intubation, at extubation, and every 6 hours thereafter through 90 hours following extubation. The primary endpoint was the drop-out (failure) rate due to lack of pain control or need for reversal of opioid effect with naloxone. Lack of pain control was defined as a score ≥ 8/20 on the Glasgow Composite Pain Scale. Non-inferiority evaluation was used to compare Recuvyra with buprenorphine (*a priori* non-inferiority margin was 15%). Secondary parameters included clinical scores for pain (Glasgow Composite Pain Scale) experienced for up to 4 days post surgery, sedation and evaluation of any side effects attributed to either of the treatments.

The drop-out rate was approximately 6% in the fentanyl-treated group and approximately 4 % in the buprenorphine group. Since the one-sided upper 97.5% confidence bound of the difference in drop-out rates was not greater than 15%, it was concluded the topical fentanyl solution was non-inferior to buprenorphine. The mean pain intensity scores decreased from 2.7 to 1.4 in fentanyl-treated dogs and from 3.1 to 1.9 in buprenorphine-treated dogs. The average pain scores in fentanyl-treated dogs were generally similar to those in the buprenorphine treated dogs at every post-surgical time point. The sum of pain intensity scores, representing pain over the entire assessment period, averaged at approximately 27 and 30 for fentanyl- and for buprenorphine-treated dogs, respectively. However, due to the very high proportion of missing data for the pain intensity scores, the value of the secondary outcomes in evaluating efficacy is doubtful.

A wide variety of anaesthetic regimens was used during the study. When employed, premedication (glycopyrrolate, acepromazine, and atropine) were used at or very near standard dosage ranges, with a majority of the dogs receiving acepromazine. Induction agents (alfaxan, propofol, thiopental and ketamine/diazepam), were used at the standard dosage ranges for both treatment groups (with the exception of diazepam, for which a lower dose was used). In both, the fentanyl and buprenorphine treatment groups, sedation scores were highest at 1 hour post-extubation, consistent with moderate sedation. Sedation scores at each consecutive assessment time decreased in both groups. Six hours after treatment dogs in both groups were only slightly sedated and the day following treatment mean sedation in both groups was nearly negligible.

Adverse events were reported for 16 fentanyl-treated dogs (15%) and 23 buprenorphine-treated dogs (22%). In the fentanyl group, 2 dogs suffered severe adverse events that were probably related to treatment and required opiate reversal. One dog in the buprenorphine group suffered a severe adverse event that was possibly related to treatment. In dogs treated with fentanyl the most frequently

reported events were emesis, bradycardia, anorexia, and sedation, occurring in 1.9-3.8 % of the treated dogs. All other events were reported at less than 1% for fentanyl-treated dogs. Reported events were generally similar to those noted in the buprenorphine group. Over the 5 day duration of study, 27% of fentanyl-treated and 28% of buprenorphine-treated dogs lost more than 5 % of their body weight. Mean temperatures were below the normal range (<37.8° C) in both groups during the first 4-6 hours but returned to within the normal range for the remainder of the assessments. Mean pulse rates in both groups were within the normal range at all assessments. Respiratory rates had a very restrictive normal range (20-40 breaths/minute), and most dogs, regardless of treatment group, fell outside this range on at least one occasion.

Soft tissue surgery

In the soft tissue surgery study (e.g. ovariohysterectomy, laparotopy, liver surgery) 119 dogs were treated with Recuvyra and 114 were treated with buprenorphine. The study protocol was similar to the protocol in the orthopaedic study (see above). The drop-out rate in the soft tissue study was 5% in the fentanyl group and approximately 2% in the buprenorphine group. Again Recuvyra was non-inferior to buprenorphine.

Over the 4 day assessment period following surgery, the mean pain intensity scores ranged from 3.3 to 1.1 in fentanyl-treated dogs and from 2.9 to 1 in buprenorphine-treated dogs. In both groups, the highest average pain intensity score occurred at 2 hours post-extubation. The sum of pain intensity scores, representing pain over the entire assessment period, averaged approximately 26 and 28 for fentanyl-treated and buprenorphine-treated dogs, respectively.

A wide variety of anaesthetic regimes within a standardised anaesthetic protocol were used during the study. In both the fentanyl and buprenorphine treatment groups, sedation scores were highest at 1 hour post-extubation, consistent with moderate sedation. Sedation scores at each consecutive assessment time decreased in both groups.

Adverse events were reported in 31 fentanyl-treated dogs (26%) and 25 buprenorphine-treated dogs (22%). In the fentanyl group 3 dogs required reversal with naloxone and a further dog which suffered profound sedation was not reversed. Two of these cases were considered to be severe adverse events. There was one severe adverse event in the buprenorphine group that was possibly related to treatment. For dogs dosed with topical fentanyl solution, diarrhoea and emesis were the most frequently reported events (7%). Sedation (lethargy), anorexia, ataxia, conjunctivitis, hypersalivation, hypothermia, and tenesmus were other reported adverse events, occurring in 1.7-5.0% of the dogs. All other events were reported at less than 1% for fentanyl-treated dogs. Over the 5 day duration of study, 31% of fentanyl-treated and 33% of buprenorphine-treated dogs lost body weight. The mean temperature and mean pulse rate were within the normal range for both the fentanyl-treated and buprenorphine-treated groups at all times. Respiratory rates had a very restrictive normal range (20-40 breaths/minute), and most dogs, regardless of treatment group, fell outside this range on at least one occasion.

Other studies

Two supportive clinical trials one on post operative pain in orthopaedic patients and another on soft tissue patients performed in US are also available. They were, however, only considered to be supportive since the positive comparator to Recuvyra was oxymorphone which is not approved in the EU.

Overall conclusion on efficacy

The applicant conducted two pivotal GCP clinical trials in the EU to investigate the efficacy of Recuvyra in controlling post-operative pain over a 4 day period following major orthopaedic and soft tissue surgery. The primary outcome was the drop-out rate due to lack of pain control or need for opiate reversal. Both pivotal field studies show that Recuvyra was non-inferior to buprenorphine in terms of pain control (measured in the drop-out rate, i.e. lack of pain control) or tolerance (need for opiate reversal).

The percentage of drop-outs was 5.8% and 5.0% for Recuvyra, and 3.8% and 1.8% for buprenorphine for orthopaedic and soft tissue surgery, respectively. The one-sided 97.5% confidence interval (CI) indicates that following soft tissue surgery, the difference in drop-out rate between Recuvyra and buprenorphine may be as many as 6.8 more per 100 dogs treated, and following orthopaedic surgery, as many as 6.3 more dogs per 100 treated.

In both studies, the one-sided 97.5% CI fell within the non-inferiority margin of 15% and therefore it was concluded that Recuvyra was non-inferior to buprenorphine in the control of post-operative pain over a 4 day period. The adverse reactions seen in the experimental tolerance studies were confirmed in the field studies. In 21% of Recuvyra and 22% of buprenorphine treated patients transient adverse events including diarrhoea, emesis, bradycardia, anorexia and hypothermia were noted.

In the EU studies overall, 2% of dogs treated with Recuvyra (compared to none of the dogs treated with buprenorphine) suffered severe adverse events that required opiate reversal.

Part 5 – Benefit risk assessment

Introduction

Recuvyra 50 mg/ml transdermal solution contains the active substance fentanyl. Fentanyl is approved in a combination product for use in small mammals in some EU member states, but is a new active substance for use in the dog. Recuvyra is indicated for the control of post-operative pain associated with major orthopaedic and soft tissue surgery in dogs.

Benefit assessment

Direct therapeutic benefit

The applicant has provided information that demonstrate satisfactorily that fentanyl exerts analgesic action by acting as a full μ-opioid receptor agonist.

Clinical efficacy of Recuvyra was demonstrated in two pivotal GCP clinical trials in the EU in controlling post-operative pain in dogs over a 4 day period following major orthopaedic and soft tissue surgery. Both pivotal field studies show that Recuvyra was non-inferior to buprenorphine in terms of pain control (measured in the drop-out rate, i.e. lack of pain control) or tolerance (need for opiate reversal).

Additional benefits

For dogs suffering longer term pain following major surgery where opiates are indicated as part of the analgesic strategy, currently authorised products need to be administered by repeated injections which may not be administered sufficiently frequently resulting in further initial discomfort following major surgery. Recuvyra would be advantageous for these cases as pain relief is continuous, and administration requires minimal intervention by the veterinarian. Recuvyra improves the currently

limited availability of opiate analgesics for veterinary use and provides a formulation of fentanyl more appropriate for veterinary medicines than the often used fentanyl patches authorised for human use (but used under the cascade in dogs).

The use of the specially designed syringe applicator has been proposed to assist delivery of the solution directly to the skin surface (avoiding application to the animal coat), and the accuracy of the dosing device is considered acceptable.

Risk assessment

Risk to humans

The risks to the operator are from accidental skin, eye or oral exposure during the administration of the product, and handling of treated animals in the surgical environment. The risks to the dog owner, their family (and other household pets) relate to direct contact with the application site (i.e. the risk of residues of the active ingredient) during the first 72 hours post-application.

Possible adverse effects in humans include sleepiness, sedation and particularly respiratory depression which can be potentially serious or even lethal.

Risk to animals

Adverse reactions seen in target animal studies and the field studies showed that Recuvyra in the RTD of 2.6 mg/kg showed typical signs of the secondary pharmacological effects of opiates: mild-moderate sedation, hypothermia, bradycardia, decreased respiratory rate, anorexia, weight loss, diarrhoea. Generally, the incidence of adverse events was similar for dogs treated with Recuvyra and the authorised product, containing buprenorphine. Opiate reversal was administered in 2% of dogs treated with Recuvyra (as compared to 0% of cases treated with buprenorphine. Fatal adverse events were recorded when Recuvyra was administered at 2X RTD repeated after 4 days, when there was no supportive care. Death was as a result of renal failure secondary to shock produced by gastrointestinal stasis.

The applicant has not presented data on the reproductive safety of fentanyl in the target species.

Risk management or mitigation measures

Humans

The operator safety is mitigated by the warnings in the SPC, particularly with reference to the personal protective equipment recommended when handling the product. The risk is further controlled by the professional status of the operators, as the product will only be used in a clinical setting, and veterinarians using Recuvyra will receive special training by the applicant on the safe use of the product prior to use.

With regard to the risk to the animal owner, direct contact to the application site should not pose any risk to adults, once the application site is dry. However, for children such contact might result in fentanyl exposure, and the SPC therefore carries a clear warning that small children should not touch the dog for 72 hours after administration, i.e. until the time of risk is over. Also, as an additional precaution, dogs with a bodyweight of 20 kg or more should remain hospitalised for 48 hours following application to further minimise the risk of exposure to children. At discharge from the clinic, the veterinarian will provide the animal owner with written instructions on the time until when a child can safely touch the dog again. Since the product is only to be used in dogs having major surgery, which are usually not admitted home soon after surgery, CVMP considered that veterinarians and animal owners would be expected to comply with this request.

The applicant has included a number of additional user warning statements in the SPC and product literature that provide additional information to the pet owner. These warnings adequately address user safety.

Animals

The most serious potential adverse events in the target species resulting from long term administration of fentanyl is death which results from shock and gastrointestinal stasis, exacerbated by sedation and failure to eat and drink. However, deaths only occurred in laboratory tolerance studies when Recuvyra was administered at 2X RTD, repeated after 4 days, and no supportive care was provided. There were no mortalities in the field studies.

Evidence from the target animal safety studies suggests that adverse reactions that do not involve severe overdose can be managed with supportive care alone without opiate reversal. Regardless, there may be circumstances where opiate reversal is preferred, and it was used in approximately 2% of dogs in the EU field studies, therefore the SPC recommends to the veterinarian that the availability of an opiate antagonist should be considered before using Recuvyra (section 4.5).

Such risks can be adequately mitigated by SPC warnings (sections 4.5, 4.9, 4.10), and include guidance to achieve accurate dosing and not to repeat the dose within 7 days; advice that dogs should not be discharged to owners until post-operative sedation is mild/absent, and animals are eating and drinking appropriately. Advice is provided on supportive care, and on administration of naloxone to reverse adverse opiate effects, if required; and commonly occurring adverse reactions (section 4.6). Advice is also provided regarding provision of supportive care and the need for eye lubrication.

The product is contraindicated for use in animals with cardiac failure, hypotension, hypovolaemia, respiratory depression, hypertension, epilepsy, corneal pathology and paralytic ileus (section 4.3). Based on the demographics of the population recruited to the field studies, there are SPC warnings not to use the product in animals with signs of systemic illness, and that safety has not been established in dogs less than 6 months of age (section 4.5). Recuvyra is contraindicated from use in pregnant and lactating bitches or breeding animals (section 4.3, 4.7). Warnings are provided regarding potential drug interactions and in relation to the anaesthetic-sparing properties of fentanyl (sections 4.5 and 4.8).

The CVMP expressed some concern in regard to the novel type of the product in veterinary medicines (long acting transdermal administration of an opoid), and the uncertainty about possible interactions of other medicines used concomitantly peri- and postoperatively with Recuvyra. The applicant has therefore committed to provide an augmented pharmacovigilance reporting system in a representative number of dogs.

Environment

The use of Recuvyra is not expected to pose a risk for the environment when used in accordance with the SPC.

Evaluation of the benefit risk balance

Any risks identified in regard to the quality data for the Recuvyra dossier have been satisfactorily resolved and appropriately mitigated in the SPC. User safety and environmental risks have also been satisfactorily addressed through the warnings in the SPC.

Recuvyra has been shown in field trials to be non-inferior to buprenorphine in the control of post-operative pain associated with orthopaedic and soft tissue surgery in dogs. An additional benefit is that the product has been formulated so that a single, non-invasive application provides continuous

analgesia over a 4 day period, aiding compliance. There is currently limited availability of opiate analgesics on the veterinary market, and those that are available are relatively short-acting (up to 6 h) and therefore have to be administered frequently to dogs with protracted pain. The benefits of Recuvyra are balanced against a risk that approximately 2% of dogs may require opiate reversal, and the general undesirable effects of opiate analgesics (e.g. sedation), which occurred at a similar incidence as following treatment with buprenorphine.

Recuvyra has been investigated in clinical trials with dogs undergoing major surgical procedures that would be associated with pain of a duration of at least 4 days, and the indication is therefore restricted to use in dogs that have undergone major procedures and when 4 days duration of analgesia is required. Risks were satisfactorily managed in the field trials, and it is considered that they can also be mitigated adequately in practice use through SPC warnings. The benefit:risk for the indication described in the target species is therefore considered to be favourable.

With regard to remaining concerns in regard to this novel type of product in veterinary medicines and the uncertainty about possible interactions of other medicines used concomitantly peri- and postoperatively with Recuvyra, pharmacovigilance requirements were increased for Recuvyra.

Conclusion

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded by majority that the quality, safety and efficacy of Recuvyra were considered to be in accordance with the requirements of Directive 2001/82/EC, as amended, and that the benefit-risk balance was favourable.

In addition, the CVMP has recommended conditions for marketing authorisation and product information:

To address the safety concerns remaining in relation to the novel type of product, and the uncertainty about possible interactions of concomitantly used products during the operation and in the post-operative period, the marketing authorisation holder should arrange for collation and assessment of detailed data on the clinical safety of the product in a representative sample of dogs. Such data will be submitted to the Agency together with the periodic safety update reports.