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Veterinary Medicines Division

## Committee for Medicinal Products for Veterinary Use (CVMP)

# Withdrawal assessment report for Somnena (EMEA/V/C/004293/0000)

International non-proprietary name (INN): buprenorphine

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

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# Introduction

On 29 January 2016 the applicant Shernacre Enterprise Limited submitted an application for a marketing authorisation to the European Medicines Agency (EMA) for Somnena in accordance with Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the Committee for Medicinal products for Veterinary Use (CVMP) on 8–10 September 2015 under Article 3(2)(b) of Regulation (EC) No 726/2004 (optional scope) as the applicant showed that the product would constitute a significant therapeutic/scientific innovation.

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

The applicant is registered as a micro-, small- or medium-sized enterprise (SME) pursuant to the definition set out in Commission Recommendation 2003/361/EC.

Somnena is a prolonged-release solution for injection containing 3 mg/ml buprenorphine (as the hydrochloride) as the active substance. The primary pack is a clear glass multidose vial containing the solution for injection. The secondary (outer) pack is a cardboard carton containing one vial. The target species is the cat. The route of administration is subcutaneous use.

The applicant initially applied for the following indication: 'For the control of postoperative pain in cats for 3 days.'

On 14 September 2016, Shernacre Enterprise Limited withdrew the application on day 120 of the procedure. In its letter notifying the EMA of the withdrawal of the application, the applicant stated the reason for the withdrawal was based on the CVMP's consideration that a pivotal clinical study which evaluated the control of post-surgical pain did not reach a satisfactory end point.

### *Scientific advice*

The applicant received Scientific Advice from the CVMP on 6 November 2015 pertaining to safety and efficacy aspects of the dossier (novel excipient), but the advice was not fully followed.

### *MUMS/limited market status*

Not applicable.

# Part 1 - Administrative particulars

### *Detailed description of the pharmacovigilance system*

The applicant provided a detailed description of the pharmacovigilance system (DDPS) which fulfils the requirements of Directive 2001/82/EC. It was accepted that the applicant had the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse event occurring either in the Community or a third country. Only some minor issues were awaiting resolution at the time of withdrawal of the application.

### *Manufacturing authorisations and inspection status*

Both the active substance and the finished product were to be manufactured and packaged outside the

EU. The batch release was to be carried out by a manufacturer within the EU.

Manufacturing authorisations and good manufacturing practice (GMP) certificates were provided for all sites to be involved in the manufacturing and batch release processes.

A GMP declaration for the active substance manufacturing site was provided by the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit. A valid manufacturing authorisation and valid GMP certificate were also provided.

### *Overall conclusions on administrative particulars*

At the time of withdrawal of the application some additional information had been requested regarding the DDPS as well as to the GMP certification of the manufacturing sites located outside EEA.

## Part 2 - Quality

### *Composition*

Somnena is a non-aqueous prolonged-release solution for injection containing 3 mg of buprenorphine per ml (as 3.23 mg/ml buprenorphine hydrochloride) and three excipients.

### *Containers*

The product was to be presented as a multidose product in a type I clear glass vial closed by an elastomeric stopper with an aluminium seal. Each vial was to be supplied in a cardboard box.

At the time of withdrawal of the application some questions had been raised.

### *Development pharmaceutics*

The objective of the pharmaceutical development program was to develop a prolonged-release solution for injection of buprenorphine.

The product is non-aqueous. The hydrochloride salt of buprenorphine was selected because of its solubility.

Pharmaceutical development had focused on the selection, and quantities of, a biodegradable liquid polymer and biocompatible solvent to effect the prolonged release of the active substance in an injectable solution formulation. A novel excipient (that is, not previously used in an EU-authorised product), was selected because of its biological (*i.e.* biodegradable and biocompatible) and physico-chemical properties, and the solvent was selected because of its biocompatibility and safety.

As the product is designed as a prolonged-release dosage form, the applicant had discussed its release pattern with reference to *in vivo* and *in vitro* testing.

The chosen sterilisation method (sterile filtration and aseptic manufacture) was justified.

The formulation used during clinical studies was the same as that intended for marketing.

In view of the possibility of large numbers of doses being withdrawn from a vial, tests for fragmentation and self-sealing of the closure were carried out.

At the time of withdrawal of the application several questions had been raised in relation to some of the above issues.

## *Method of manufacture*

Detailed descriptions of the proposed commercial batch size and the production steps were provided. The manufacturing process consists of 4 main steps: 2 mixing steps of the components, sterile filtration, filling into the vials (prewashed and depyrogenated) with nitrogen purging, then sealing the vials with the stoppers and aluminium caps (both presterilised by autoclaving). All the steps are performed under aseptic conditions.

In line with the CVMP guideline on process validation for finished products (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1) the method is considered to be a non-standard manufacturing process as the finished product is a modified release preparation and filling is performed under aseptic conditions.

At the time of withdrawal of the application several questions had been raised in relation to some of the above issues.

## *Control of starting materials*

## *Active substance*

Buprenorphine hydrochloride is the subject of a monograph in the European Pharmacopoeia (Ph. Eur.). A valid certificate of suitability (CEP) issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM) was provided for the named manufacturing source of the active substance. The control tests carried out by the active substance manufacturer comply with the specifications and test methods of the Ph. Eur. monograph and additional tests of the CEP.

Batch analysis data had been provided, and the results were within the specifications.

The CEP states a re-test period of the active substance when stored in double polyethylene bags placed in a cardboard or polyethylene drum.

At the time of withdrawal of the application two questions had been asked regarding the active substance.

## *Excipients*

Three excipients are used in the formulation.

Two excipients comply with the requirements of the relevant Ph. Eur. monographs.

Some satisfactory information was provided on the manufacture and control of the novel excipient but at the time of the application's withdrawal, several questions had been raised in relation to this excipient.

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

None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01-Rev.3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

## *Control tests during production*

Not applicable.

## *Control tests on the finished product*

Descriptions of the proposed specifications for use at release and at the end of shelf-life were provided. However some further information was required before a final conclusion could be made on their acceptability.

The internal analytical methods were largely adequately described and appropriately validated in accordance with the relevant VICH guidelines, although one method appeared to require further modification and a question was therefore raised. Satisfactory information regarding the reference standards had been presented.

Batch analysis results were provided for 3 pilot scale batches. But the consistency of the manufacturing process and its ability to manufacture to the intended product specification needed some further confirmation.

At the time of withdrawal of the application several questions had been raised in relation to some of the above issues.

## *Stability*

Stability data for 3 pilot scale batches of the finished product stored under long-term conditions for 24 months at 25 ºC/60% RH and at 5±3 °C, and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH GL3 on stability testing of new veterinary drug substances and medicinal products (CVMP/VICH/899/99 Rev.1) were provided. The batches of Somnena used were representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested using the methods of the finished product specification. The analytical procedures were stability indicating.

On the basis of the data provided, the proposed shelf-life could have been accepted provided that a few questions raised were satisfactorily answered.

In the absence of any photostability data, the vial should remain in the outer cardboard box and an appropriate warning to protect the product from light would therefore have needed to be added to the proposed SPC.

Similarly, unless satisfactory freeze/thaw cycle data were provided, additional suitable precautionary warnings against low-temperature storage (freezing) would also have needed to be added to the proposed SPC.

At the time of withdrawal of the application, no in-use shelf-life could be agreed for the product as questions were raised on the in-use study data provided.

## *Overall conclusions on quality*

In general the dossier provided a suitable description of the formulation of the product and demonstrated that the manufacturing process would lead to a stable product with consistent quality, although questions had been raised which would have needed to be satisfactorily addressed before the quality part of the application could have been considered acceptable.

The development pharmaceutics of the formulation had been explained.

The manufacturing process is non-standard in that the finished product is a specialised pharmaceutical dose form and it involves aseptic processing, although this had been suitably justified. However, validation data would have been required before authorisation. Some other issues required further clarification.

The active substance is sourced in accordance with a valid EDQM certificate of suitability.

The polymer is not described in any pharmacopoeia and has not been used previously in an EU-authorised veterinary medicinal product so is considered novel. Although the data package to support its use is generally satisfactory some additional assurances were required. The two other excipients are the subject of current Ph. Eur. monographs.

The packaging materials are standard although some additional data were required.

No material of animal origin is used in the manufacture of Somnena.

The proposed finished product specification includes most of the relevant quality attributes and the internal control methods are described and appropriately validated; however, some further information was required on some test methods.

Certificates of analysis were provided for three pilot scale batches manufactured at the site proposed for commercial manufacture.

Stability studies on the finished product were performed under VICH conditions, and the data support the proposed shelf-life, although a few issues required resolution. The necessary storage precautions had not been fully addressed by the time of withdrawal of the application. Likewise, the claimed in-use shelf-life required justification.

In conclusion, a number of quality issues required to be addressed by the applicant before a conclusion regarding the quality of the product could be made.

# Part 3 – Safety

The active substance in Somnena, buprenorphine hydrochloride, an opioid, has been used in human and veterinary medicines for several years. However, the novel excipient has not been used in an EU-authorised veterinary medicinal product before. Scientific Advice from the CVMP was sought by the applicant on the safety data requirements for this excipient.

The applicant did not perform any toxicological studies with buprenorphine, but numerous references from the open literature were provided. In addition, new data were provided regarding the novel excipient.

## *Safety documentation*

## *Pharmacodynamics*

See Part 4.

## *Pharmacokinetics*

See Part 4.

## *Toxicological studies*

While no toxicological studies have been conducted with buprenorphine by the applicant, the published data provided corroborate what is known about the toxicological profile of this substance, which is currently used in human and veterinary medicinal products.

### Single dose toxicity

No acute toxicity studies were conducted with buprenorphine by the applicant. Much of the development work on buprenorphine was carried out prior to the introduction of GLP; however, the age of the data does not detract from its integrity, and the provided studies were well conducted and well reported.

In the open literature, acute studies in rodents using a variety of routes of administration have indicated very low acute toxicity of buprenorphine after oral and subcutaneous administration (oral $LD_{50}$ close to 300 mg/kg bw, subcutaneous $LD_{50}$ > 300 and 600 mg/kg bw in mouse and rat, respectively). A higher acute toxicity was noted after intravenous administration ($LD_{50}$ in the 25 mg/kg bw range). The main adverse effects seen were related to the pharmacological activity of buprenorphine, as an opioid, and consisted of neurological symptoms (convulsion, changes in motor activity) and cardio-respiratory failure.

### Repeat dose toxicity

Bibliographic references were provided in relation to the repeat dose toxicity of buprenorphine.

Following oral and subcutaneous administrations for 1 month and intramuscular administrations for 6 months to rats, a treatment related (but not dose-related) decrease in body weight gain was the only abnormality recorded, with similar observations being reported in dogs and monkeys. Intramuscular doses of 0.5 or 5 mg/kg bw/day buprenorphine (over 6 months) in monkeys resulted in some haematological changes associated with inflammation at injection site at 5 mg/kg bw/day. This effect was not observed at 0.05 mg/kg bw/day.

Neither mortality nor organ toxicity was seen in 90-day toxicity studies in rats and dogs at doses up to 5 and 2.5 mg/kg bw/day, respectively.

No suitable no-observed-effect level (NOEL) has been determined from the data provided (see below).

## *Tolerance in the target species of animal*

See Part 4.

## *Reproductive toxicity*

### *Study on the effect on reproduction*

No studies on the effects on reproduction of buprenorphine have been conducted by the applicant.

A reference from the public domain showed that subcutaneous administration of buprenorphine had no effects on fertility or general reproductive performance in rats at exposure levels as high as 100 to 152 times that of human subjects who received 20 µg buprenorphine/h via a transdermal device.

### *Study of developmental toxicity*

No studies for possible effects of buprenorphine on development were conducted by the applicant;

however, numerous bibliographic references were provided.

Pregnant rats were subcutaneously implanted with a mini-pump containing buprenorphine from D7 or D8 of gestation through to parturition at doses of 0.3, 0.1 or 3 mg/kg bw/day. Maternotoxic effects were reported at all tested doses (reduction in food/water intake, reduction of weight gain), including at the lowest dose of 0.3 mg/kg bw/day. Fœtotoxicity (increased foetal mortality due to increased number of resorptions) was noted.

In pregnant rats subcutaneously administered 0.3 mg/kg bw/day buprenorphine from D3 of gestation to D20, reduced body weight gain and prenatal mortality were reported.

Female rats intramuscularly administered 0.05, 0.5 or 5 mg/kg bw/day buprenorphine from D17 of gestation to D21 postpartum showed reduced food and water intake at 5 mg/kg bw/day. A slight depression of body weight gain was reported at all tested doses.

It is clear from these publications that, in pregnant female rats, maternotoxicity occurred from 0.3 mg/kg bw/day or from 0.05 mg/kg bw/day, after subcutaneous or intramuscular administration of buprenorphine, respectively. This point is crucial as 0.3 mg/kg bw/day is the claimed dose for Somnena in cats. Thus, as the safety of the product has not been assessed in pregnant queens, the use should be contraindicated during pregnancy. A respiratory depressive effect of buprenorphine of peri-parturient offspring could not be excluded. The safety of the product, when used pre-operatively for caesarean section, has not been assessed in queens. This further supports the contraindication during pregnancy. A contraindication would need to have been added in the proposed SPC.

In one reference it was reported that buprenorphine was not teratogenic and had no effect on reproductive capacity, duration of gestation or parturition in rodents (doses not stated). However, an increase in foetal deaths and increased pup mortality was seen. Buprenorphine affects the milk production which could be related to pup mortality.

Thus, the provided data allow the conclusion that embryotoxicity/foetotoxicity were reported only at maternotoxic doses and that buprenorphine is not teratogenic.

It should be noted that none of the provided studies was conducted according to OECD guideline 414 (prenatal developmental toxicity study). However, the toxicological profile of buprenorphine, including the reprotoxic potential was considered as sufficiently documented.

As buprenorphine crosses into milk and affects milk production, and as the safety of the product has not been assessed in lactating queens, the use of the product during lactation should have been contraindicated (and referred to in the SPC).

### *Genotoxicity*

No genotoxicity tests were performed with buprenorphine by the applicant.

Data on the genotoxic potential of buprenorphine were provided from relevant published literature.

In 3 genotoxicity assays using buprenorphine (assay for bacterial gene mutation, test for chromosomal damage on human lymphocytes *in vitro*, and rat micronucleus test *in vivo*) negative results were recorded.

The non-genotoxic potential of buprenorphine was confirmed in 4 other genetic toxicology studies - bacterial mutagenicity test, mouse lymphoma assay, chromosomal aberration assay in human peripheral blood lymphocytes and an *in vivo* mouse micronucleus test.

Based on the provided information, it was concluded that buprenorphine is not genotoxic.

## *Carcinogenicity*

No carcinogenicity studies with buprenorphine have been performed. Data from published literature were provided.

Testicular interstitial (Leydig) cell tumours were reported in rats after oral administration of buprenorphine. Such findings were not observed in other species. The toxicological significance for human and other animal species had not been fully explained at the time of the application's withdrawal.

The frequencies of other malignant lesions observed in rats were within the historical control range.

## *Studies of other effects*

### Human data

Buprenorphine is widely used in human medicine for the treatment of moderate to severe pain and the treatment of opioid dependency. The applicant submitted data from numerous literature references about injectable products (intravenous or intramuscular administration), sub-lingual tablets, and a transdermal patch. The reported adverse effects in humans were: reduction in respiration rate and blood pressure, impairment of psychomotor performance, sedation, gastrointestinal disturbances (nausea, vomiting, and constipation), headache, and dizziness.

Cases of hypersensitivity to buprenorphine have been reported in clinical trials for marketed buprenorphine products. The most common adverse effects were rashes, hives and pruritus. Cases of bronchospasms, angioneurotic oedema and anaphylactic shock, have been reported. As a result, a warning was included in the proposed SPC.

As buprenorphine is transferred across the placenta to neonates and is transferred via the breast milk at a similar concentration to that found in maternal plasma, the inclusion of a warning in the SPC in case of handling by a pregnant/breast-feeding user (veterinarian) might also need to have been considered if the application had not been withdrawn.

### Excipients

Polymer

Because the polymer had not previously been used in a veterinary medicinal product, the applicant had requested CVMP Scientific Advice regarding the safety of this excipient, before the application had been submitted.

No repeat-dose studies or reproductive toxicity studies were provided in relation to the novel excipient. However, as it is similar to commonly used aliphatic polyesters, the excipient can be considered to be of low toxicity. Furthermore, they are known to degrade *in vivo* to produce biocompatible, toxicologically safe by-products, which are further eliminated by the normal metabolic pathways.

The applicant performed a QSAR analysis to study the genotoxic potential of the novel excipient. Negative results for genotoxicity and carcinogenicity were recorded for the first monomer in three different models (VEGA, T.E.S.T and OECD toolbox). This absence of genotoxic potential is confirmed in OECD SIDS, 2004, in which the first monomer gave negative results in bacterial and mammalian in vitro mutagenicity tests and in a mouse micronucleus assay. In the same publication, the first monomer is reported to be non-reprotoxic, non-irritating for skin but irritating for eyes.

With the same models, overall ambiguous results were obtained for the second monomer (positive results with VEGA, 1 out 3 positive results with T.E.S.T). Negative results were obtained with the OECD

toolbox. In addition, VEGA and T.E.S.T models are reported to give numerous false negatives. Hence, it was not possible to definitely conclude about the genotoxic/carcinogenic potential for the second monomer, and consequently for the novel excipient.

It should, however, be noted out that the hydrolysis of the polymer in the body would release substances that are devoid of genotoxic/mutagenic potential. Thus, after metabolism, the novel excipient should not have any genotoxic/mutagenic potential.

The metabolism of the excipient possibly also generates another metabolite from the lateral chain of the component. Information on this metabolites toxicity remained to be provided.

The possibility that the inflammatory reaction induced by the novel excipient may cause the occurrence of a fibrosarcoma in predisposed cats could not be ruled out. This risk had not been addressed by the applicant at the time of withdrawal.

Evidence that the co-polymer is metabolised and excreted safely from the cat was requested. At the time of withdrawal of the application the data had not been provided.

Another of the excipients in Somnena and the nitrogen used during manufacture are currently used in human and veterinary medicinal products. The toxicological profiles of both substances have been suitably addressed. The excipient can induce erythema or contact dermatitis after prolonged and intensive skin contact.

The applicant provided toxicological data on a substance which is not one of the excipients in the product. This was not acceptable as data on the specific excipient is available in the public literature. The specific compound is classified as a reprotoxic substance 1B (presumed to be toxic for human reproduction) under the CLP regulation. The applicant was therefore requested to provide toxicological data on this excipient. These data were not provided at the point the application was withdrawn.

### *User safety*

Although a user safety risk assessment was presented, it had not been conducted strictly in accordance with the CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1).

The most likely potential route of exposure would have been dermal due to contact with any product left in the dosing syringe, but it could also be expected that ocular or oral exposure due to hand to mouth contact may occur. The potential route of exposure of most concern was via accidental self-injection. Because the product was intended to be used only by a veterinarian and to be stored only in a veterinary clinic, it was not considered necessary to assess the risk to children.

The applicant had proposed a worst case self-injection scenario in which only the volume of product within the needle itself (0.1 ml) was injected. This was not accepted by the committee as a worst case scenario since at least some of the contents of the syringe could also be (accidentally) injected and a larger volume should, therefore, have been used to assess the exposure. This risk had not been adequately addressed by the applicant at the time of withdrawal.

Dermal irritation and sensitisation studies and ocular irritation studies with Somnena had not been conducted. However, there are suitable data in the published literature which enable the qualitative risk to be evaluated: Somnena is a potential skin and eye irritant. Suitable warnings should, therefore, have been included in the proposed SPC.

The toxicological data provided did not allow a full quantitative risk assessment to be conducted for the product since no no-observed-adverse-effect level (NO(A)ELs) had been determined and the applicant

proposed to use toxicological endpoints from the target animal safety (TAS) studies. This approach is not acceptable as the TAS study did not determine a NOEL, which is recommended in the current CVMP guideline for user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/2003 Rev. 1), and the value proposed by the applicant as the NOEL (0.3 mg/kg) should not be considered as such, because adverse effects are reported even at the lowest tested dose.

The applicant would need to provide suitable toxicological data on the components of this product, which include the determination of NO(A)ELs, in order for this scenario, in particular, to be assessed. Such data might have come from short-term studies (as accidental self-injection is likely to be a single incident, and not often repeated), and should, if possible, have come from publicly available literature.

The toxicological data provided on one of the excipients were mostly based on read-across from similar molecules; however, there are more relevant data on the excipient itself, including international reviews of the data, available in the public domain that would have been more suitable for use in the URA.

It was identified that the novel excipient breaks down *in-vivo* into several, relatively non-toxic components; however, for one of these components no data were provided. Such data should have been provided and incorporated into the user risk assessment.

Exposure

For the reasonable worst-case exposure, 0.8 ml of the product should have been used when conducting the risk assessment. Once margins of exposure for each component were determined, suitable risk mitigation measures might then need to have been considered.

The applicant had received Scientific Advice pertaining to safety aspects of the dossier (novel excipient), but the advice was not fully followed.

The applicant should have considered the fact that the extended release of the active ingredient, which is due to the novel excipient, would cause a longer duration of effect on the user in case of accidental injection; however, this aspect had not been addressed at the point the application was withdrawn. It was stated that the treated cats would be sedated before treatment, but this was not considered to be likely. This would have needed to be discussed in relation to the risk of exposure of the veterinarian that will be handling the animals and the product.

Risk communication

Based on the revised URA, user safety warnings in line with the ABCD format recommended in the CVMP Guideline EMA/CVMP/543/03-Rev.1 should have been proposed.

As buprenorphine is transferred across the placenta to neonates and is transferred via breast milk at a similar concentration to that found in maternal plasma, and as one of the excipients is classified as a reprotoxic substance 1B, a warning in the case of handling by a pregnant/breast feeding women (veterinarian) should have been considered.

## *Environmental risk assessment*

A Phase I environmental risk assessment was provided in line with VICH GL6 (Environmental Impact Assessment for Veterinary Medicinal Products - Phase I) (CVMP/VICH/592/98-FINAL). Given that the product was for the treatment of cats, the environmental risk assessment could stop at Phase I.

The product was not expected to pose a risk to the environment when used according to the proposed SPC.

## *Overall conclusions on the safety documentation*

While no new toxicological studies were conducted with buprenorphine by the applicant, the published data provided corroborated what was already known about the toxicological profile of this substance, which is currently used in human and veterinary medicine.

Acute studies in rodents have indicated a very low acute toxicity of buprenorphine after oral and subcutaneous administration. A higher acute toxicity was noted after intravenous administration ($LD_{50}$ in the 25 mg/kg range). Main effects were related to the pharmacological activity of buprenorphine as an opioid and consisted of neurological symptoms (convulsion, changes in motor activity) and cardio-respiratory failure.

Following oral and subcutaneous administrations for one month and intramuscular administrations for 6 months to rats, a decrease in body weight gain was the only abnormality recorded, with similar effects being reported in dogs and monkeys. Intramuscular doses of 0.5 or 5 mg/kg bw/day buprenorphine (over 6 months) in monkeys resulted in some haematological changes associated with inflammation at the injection site at 5 mg/kg bw/day. This effect was not observed at 0.05 mg/kg bw/day.

Neither mortality nor organ toxicity was seen in 90-day toxicity studies in rats and dogs at doses up to 5 and 2.5 mg/kg bw/day, respectively.

No NOEL has been determined from the toxicological data provided.

Numerous bibliographic references from open literature were provided on developmental toxicity. These data concluded that embryotoxicity/foetotoxicity were reported only at maternotoxic doses and that buprenorphine is not teratogenic.

It should be pointed out that in pregnant female rats, maternotoxicity occurred from 0.3 mg/kg bw/day or from 0.05 mg/kg bw/day, after subcutaneous or intramuscular administration of buprenorphine, respectively. As 0.3 mg/kg bw/day was the proposed dose for Somnena in cats and as the safety of the product had not been assessed in pregnant queens, use of the product would not have been able to be recommended during pregnancy. In addition a respiratory depressive effect of buprenorphine of peri-parturient offspring could not be excluded. The safety of the product when used pre-operatively for caesarean section had not been assessed in queens. This observation supported a proposed contraindication for pregnant queens.

As buprenorphine crosses into milk and affects milk production, and as the safety of the product had not been assessed in lactating queens, the use of the product during lactation would have been contraindicated.

Buprenorphine was not genotoxic in a relevant battery of mutagenicity tests. In carcinogenicity studies in rats, testicular interstitial cell tumours were reported. The relevance of these tumours for other species has not been fully explained.

A copolymer excipient in the product has never been used in a veterinary medicinal product authorised in the EU. The applicant performed a QSAR analysis for the genotoxic potential of the monomers. Ambiguous results were obtained for the genotoxic potential of one monomer. However, it should be pointed out that the hydrolysis of the polymer in the body would then release three metabolites. These substances are devoid of genotoxic/mutagenic potential. Thus, after metabolism, this excipient should not have any genotoxic/mutagenic potential.

No evidence that the copolymer is metabolised and excreted safely from cats has been provided. At the time of withdrawal of the application the applicant had been asked to address some questions.

The user risk assessment provided was not strictly conducted in accordance with CVMP guideline EMEA/CVMP/543/03-Rev.1. Exposure scenarios, users (only veterinarians), main routes of exposures (dermal, ocular, parenteral) and probability of occurrence were well identified. Because the product was intended to be used only by a veterinarian and to be stored in a veterinary clinic, there was no need to assess the risk for children. There are suitable data in the published literature which enabled the qualitative risk of the product to be evaluated: it is a potential skin and eye irritant and a dermal sensitizer. The quantitative risk characterisation had not been correctly performed, as the volume that might have been self-injected had not been suitably chosen and, as used, the toxicological endpoints were not in accordance with the recommendation of the CVMP guideline EMEA/CVMP/543/03-Rev.1. In addition, in the URA, the applicant implied that in all cases the cat would be sedated, although this recommendation did not appear in the proposed SPC. At the time of withdrawal of the application this issue would need to have been addressed, a new risk characterisation required and the proposed risk mitigation measures revised.

At the time of withdrawal, a question remained to be addressed regarding the fact that the extended release of the active ingredient, which is due to the novel excipient, would cause a longer duration of effect on the user in case of accidental injection.

In addition, as buprenorphine is transferred across the placenta to neonates and is transferred via breast milk at a similar concentration to that found in maternal plasma, the need for a warning in the case of handling by a pregnant/lactating user (veterinarian) was also questioned.

A Phase I environmental risk assessment was provided in line with VICH guideline GL6 (Environmental Impact Assessment for Veterinary Medicinal Products - Phase I) (CVMP/VICH/592/98-FINAL). Given that the product was for the treatment of cats, the environmental risk assessment could stop at Phase I. The product was not expected to pose a risk to the environment when used according to the proposed SPC.

In conclusion, a number of safety issues required to be addressed by the applicant before a conclusion regarding the safety of the product could be made.

# Part 4 – Efficacy

## *Pharmacodynamics*

No pharmacodynamic studies were provided, but as the mode of action of the active substance is well known; reference to published literature was made. Buprenorphine is a potent, long-acting analgesic and it exerts its analgesic effect via high- affinity binding to various subclasses of opiate receptors, particularly in the central nervous system. At clinical dose levels established for analgesia, buprenorphine demonstrates high efficacy and binds to opiate receptors with high affinity, such that its dissociation from the receptor site is slow, as demonstrated in *in vitro* studies. This property of buprenorphine could account for its longer duration of activity when compared to morphine. In circumstances where excessive opiate agonist is already bound to opiate receptors, buprenorphine can exert a narcotic antagonistic activity as a consequence of its high-affinity opiate receptor binding, such that an antagonistic effect on morphine equivalent to naloxone has been demonstrated. Buprenorphine has little effect on gastrointestinal motility.

One behavioural study in cats with a non-final formulation administered once at 0.3, 0.6 and 0.9 mg/kg bw by the subcutaneous route was provided. At all three dose levels cats demonstrated behavioural evidence of an opiate effect, i.e. mydriasis.

## *Pharmacokinetics*

Three non-GLP pharmacokinetic studies were provided; conducted in cats after administration of a single subcutaneous dose of 0.3 mg/kg bw buprenorphine in an extended release formulation. Two out of the 3 studies were conducted with the final formulation. Furthermore, single blood samples were collected in a non-GLP tolerance study with the final formulation.

The results of the pharmacokinetic studies provided evidence of significant inter-individual variations in plasma buprenorphine concentration between cats. Following single subcutaneous administration of the formulation at 0.3 mg/kg bw, plasma buprenorphine concentrations rose slowly reaching a $C_{max}$ of 1.33 to 5.35 ng/ml after 12 to 60 hours. This was followed by a slow decline in concentration, with plasma buprenorphine levels remaining above 1 ng/ml until 72 hours post-administration. The $t_{1/2}$ of the product was 14.8 hours.

In tissue distribution studies carried out in rats and Rhesus monkeys, the highest concentrations of drug-related material were observed in the liver, lung and brain.

The major route of excretion in all species except the rabbit (where urinary excretion predominates) is the faeces. Buprenorphine undergoes N-dealkylation and glucuronide conjugation by the intestinal wall, and the liver and its metabolites are excreted via the bile into the gastro-intestinal tract. Studies have reported that both buprenorphine and norbuprenorphine are excreted in the faeces.

## *PK-PD (dose justification)*

The applicant considered that a buprenorphine plasma concentration of 1 ng/ml is considered analgesic in humans, rat and mice. In this application, no study using a model of induced pain was conducted to establish the threshold for pain control in cats, and the applicant justified the proposed dose on the basis of PK-PD calculations, using a plasma level of 1 ng/ml as the threshold for the required analgesic effect. During the two studies performed using a single subcutaneous dose of 0.3 mg buprenorphine/kg bw, plasma buprenorphine concentrations reached the threshold of 1 ng/ml in 100% of the cats at 24 hours after administration and stayed above 1 ng/ml until 72 hours after administration.

However, published literature (Steagall, 2013) suggests that: “a large initial concentration gradient of buprenorphine may be needed in order to drive the drug into the biophase”. Following this hypothesis, the proposed plasma level might not be sufficient, and other authorised veterinary medicinal products containing buprenorphine for cats might be more efficacious since they lead to higher $C_{max}$, (e.g. Vetergesic leads to a median $C_{max}$ of 8.7 ng/ml [range: 3.6 to 11.8 ng/ml] after IM injection of 0.01 mg buprenorphine/kg bw (Taylor, 2001).

Also, there is a poor correlation between antinociception and the plasma concentration of buprenorphine after IV and IM administration (Steagall et al., 2014). This is also noted in the SPC of some authorised veterinary medicinal products containing buprenorphine for use in cats which state that: “Combined pharmacokinetic and pharmacodynamic studies have demonstrated a marked hysteresis between plasma concentration and analgesic effect. Plasma concentrations of buprenorphine should not be used to formulate individual animal dosage regimens, which should be determined by monitoring the patient’s response”. However, the SPCs of these already authorised products also specify a recommended dosing scheme and provide some useful information as regards the time of onset, the time of peak and the duration of the analgesic effects. This was missing in the proposed SPC for Somnena.

In conclusion, the proposed therapeutic scheme of a single dose of 0.3 mg buprenorphine/kg bw s.c. for the control of post-operative pain in cats for 3 days was not validated by PK/PD analysis.

However, establishing a dose–response relationship through PK/PD modelling may be difficult because of the individual variability of cats and the absence of correlation between plasma buprenorphine concentrations and analgesia. As a possible alternative to PK/PD modelling, well-conducted dose determination studies using an appropriate pain model may be sufficient to establish a dosing regimen without direct linkage to plasma concentrations. However, serious concerns are raised over the design and findings of the submitted dose determination study and the strategy used for selecting the dosing regimen. As a result, further data or thorough scientific justifications to support an appropriate dosing regimen are required. It should be noted that the therapeutic threshold can vary depending on the pain model and that the model should be ethical and suited to the intended indication for the veterinary medicinal product.

### *Target animal tolerance*

One pivotal tolerance study and two additional studies were provided to investigate target animal safety of the product, in addition to the safety data obtained from the clinical safety and efficacy trial(s).

One pivotal tolerance study was performed by the applicant. This study was conducted with the final formulation but was not GLP, although it was conducted in the spirit of VICH guideline GL43.

The product was administered by the subcutaneous route to healthy male and female cats (minimal age: 6.5 months; minimal weight: 2.2 kg) at 0 (saline), 1, 3 or 5 times (x) the recommended therapeutic dose (RTD) of 0.3 mg/kg bw, once every 3 days for a total of 3 administrations. Each injection was made at 3 different sites. At the time of withdrawal of the application the applicant had not yet justified the choice of duration of treatment (9 days) during the pivotal tolerance study. The applicant would have needed to explain how the duration of treatment during this study relates to the way the product would have been used in the field, bearing in mind that some hospitalised patients may have required more than one injection.

The main adverse effects were bilateral mydriasis, pain on injection, and reactions at injection sites (erythema, swelling, and discharge at injection site). They were observed at all tested doses and timepoints, with the frequency and severity increasing with increasing doses, as outlined in the table below. At 3x and 5x RTD, reactions at the injection sites also lasted longer.

| Adverse effect | Incidence | | | |
|---|---|---|---|---|
| | Control (saline) | 1x RTD | 3x RTD | 5x RTD |
| Moderate to severe pain | 0 | 25% | 83% | 92% |
| Pain for 10 or more seconds | 0% | 4% | 42% | 75% |
| Incidence of injection site erythema (all 3 sites) | 4% | 25% | 38% | 75% |
| Incidence of injection site discharge | 0% | 25% | 29% | 63% |

The main gross pathology findings related to the product were those at injection sites. They were more pronounced at 3 and 5 times the claimed dose. Histologically, these lesions appeared to be either

superficial erosive, haemorrhagic, ulcerative (5 times the claimed dose) and/or inflammatory skin lesions. The subcutaneous inflammatory lesions were sub-acute to chronic (as characterised by inflammatory cell type infiltration) and usually increased in severity with both increased dosing and time following injection.

The findings of this study would have needed to be incorporated into the SPC. At the time of withdrawal of the application the possibility that the inflammatory reaction induced by the novel excipient might lead to the development of a fibrosarcoma in predisposed cats could not be ruled out, and a question had been raised.

In a second non-GLP study, anaesthetised cats were subcutaneously administered with an extended release buprenorphine hydrochloride (0.3 mg/kg bw) formulation, with an immediate release buprenorphine (0.03 mg/kg bw) formulation, or with a negative control (saline). Each cat received the 3 products, with a 14 day wash out period between each administration. It was not clearly specified if the final formulation was used in this study.

There was no statistically significant difference between the blood pressures of the groups prior to or after anaesthesia. During anaesthesia, the mean blood pressure was approximately 10 mmHg higher in the test group than the saline group, and the difference was statistically significant. However, given that blood pressures were below normal conscious physiological levels in both groups, there was no evidence that administering the product would result in hypertension.

In a third non-GLP study, healthy cats were dosed with Somnena at the proposed recommended single dose of 0.3 mg/kg bw via subcutaneous injection, followed by administration of either butorphanol (0.4 mg/kg) or saline at 6, 12, 18 and 24 hours post dosing. Pain and bilateral mydriasis were reported after injection of both products. No signs of interactions were noted when the administration of the product was followed by an administration of butorphanol.

Overall, the tolerance studies showed that Somnena induced pain and local reactions at the injection sites (erythema, swelling, discharge) and resulted in bilateral mydriasis in one study. Frequency, severity and persistence of these reactions increased with the dose. In one study blood pressure was higher in treated cats than non-treated cats during anaesthesia, although it was below normal physiological levels in both groups (i.e. no evidence that administering the product would result in hypertension). There were no signs of interactions between Somnena and another opioid (butorphanol), subsequently administered; although the impact on the analgesic effect was not investigated. However, the three studies were not GLP-compliant, and deficiencies in the study design were identified and therefore questions raised.

Tolerance was also investigated during pre-clinical and clinical studies. Induction of bilateral mydriasis and pain upon injection was confirmed during the pre-clinical and clinical studies. In the clinical field study, two cats developed lumps at the injection site, and one cat had alopecia at the area of the injection site. Any injection site lesions should have been carefully monitored and recorded during efficacy studies until they had resolved fully. This had not been done, so at the time of withdrawal of the application, the absence of such information remained to be justified. In other field studies, respiratory depression was commonly reported in treated cats compared to placebo. This is a well-known adverse effect of buprenorphine.

At the time of withdrawal of the application it was not possible to conclude on the tolerance of the product when used as claimed, especially regarding resolution of injection site lesions caused by the product, and the possible development of fibrosarcoma. The applicant was requested to clarify some issues and to update the SPC with all the findings from the studies reported above.

## *Clinical field trials*

## *Dose determination / finding studies*

A single non-GLP, non-GCP dose titration study was conducted in cats undergoing surgery, using 3 dose levels (0.2 mg, 0.3 mg and 0.4 mg of buprenorphine HCl per kg body weight) or control (placebo-treated), administered subcutaneously as a single dose. The selection of the dose levels was meant to mimic the repeated use of an immediate release product every 8 hours over 72 hours.

The study was a 2 period crossover study with 16 cats enrolled (11 female intact/spayed and 5 male intact/castrated; 8 to 163 months; between 1.9 and 4.0 kg body weight) and allocated to 4 different treatment sequences (0.4/0.3 mg/kg; 0.3/0.0 mg/kg; 0.0/0.2 mg/kg; 0.2/0.4 mg/kg). At study conclusion, each cat had both front paws declawed, each treatment sequence had been evaluated 4 times (4 cats by treatment sequence) and each individual treatment was administered 8 times.

However, due to several concerns of over both the design and the conduct of the study, it was considered that the data supporting the RTD (recommended treatment dose) of 0.3 mg/kg were weak. Unless the dose response curve is thought to be very steep, this might be because the chosen doses were too similar to one another, and that more appropriate doses were missed. Indeed, the selected dosing regimen comes further into question-based on the inconclusive results seen in the dose confirmation and field studies (see below). A re-evaluation of the chosen dosing regimen and timing of the dose through PK/PD modelling, further dose determination studies using a pain model, or thorough scientific justification was therefore considered to be required.

## *Dose confirmation studies*

A prospective non-GLP, non-GCP proof-of-concept trial was presented as a laboratory dose confirmation study. It was not clear if the final formulation of the product was used. The dosage used was 0.6 mg buprenorphine per kg body weight *i.e.* twice the proposed RTD for Somnena of 0.3 mg/kg. Thus the study could not be considered as supportive to confirm the efficacy of Somnena 3 mg/ml solution for injection at the recommended dose. Possible adverse events were not detailed in the study report, but a significant effect on respiration was noted, with cats treated with buprenorphine at the dosage of 0.6 mg per kg of body weight having lower respiration rates than those in the control group.

## *Clinical field trials*

## *Dose confirmation*

Two GCP-compliant pilot dose confirmation studies were conducted in 2015 in the USA with the final formulation of the product in the field. The studies involved 36 healthy cats of both genders, at least 6 months old and presented to the clinic for a forelimb declaw (onychectomy) and reproductive sterilisation. Animals were housed in the veterinary clinic at a minimum from day -1 or day 0 (prior to surgery) through 72 hours post-extubation. A model of surgery combining onychectomy of forelimbs under lidocaine ring-block and either castration or ovariohysterectomy was used for assessment of post-surgical pain control. The primary efficacy variable was success percentage at day 1 (through 24 hours) with success defined as the cat not requiring rescue pain medication or removal from the study due to an adverse event. The decision to administer rescue pain relief was a subjective one (contrary to recently published validated systems using objective measurements) which could have led to a reduced ability to effectively discriminate between cats with pain and cats without pain. Also, the applicant did not specify a value for the difference between the treatment group success percentages

which could be considered clinically relevant. The choice of the primary efficacy variable (percentage of success at 24 hours) was not suitable for the demonstration of efficacy of the product for control of pain for 3 days.

Similarly to the dose determination study, the timing of the dose (30 minutes to one hour before surgery in one of the studies and 2–3 hours before surgery in the other) is questionable given that the pharmacokinetic studies indicated a $T_{max}$ of 12 to 60 hours.

For both studies, compliance with GCP is doubtful and many results were not fully reported. Based on the available results, the validity of the model is questionable and this is discussed also for the pivotal field study (see below). Indeed no obvious conclusion on the efficacy of the product could be made with these pilot studies. This could be explained by the low number of cases enrolled (8 and 10 cats treated with Somnena and 8 and 10 cats treated with a negative control product, in the first and second studies respectively), but also by a lack of sensitivity of the model, inadequate detection of pain or the lack of efficacy of the product at this time point (e.g. due to inappropriate choice of dose or dose timing). No significant difference in success rate at day 1 was observed between the treated and negative control groups (62.5% and 37.5% of success in the treated group and negative control group in the first study; 60% and 20% of success in the treated group and negative control group in the second study).

At the time of withdrawal of the application the studies could not, therefore, be considered as supportive. Regarding the safety aspects of these studies, observations at the injection site, in particular relating to pain on injection, were yet to be provided and discussed.

### *Clinical studies*

The pivotal clinical trial was performed in the USA in 2014. The trial investigated the effect of Somnena at the RTD on post-operative pain following 2 concomitant surgical procedures in cats: onychectomy with castration or onychectomy with ovariohysterectomy. This was a GCP-compliant study performed at 8 different study sites. For the study design see the table below.

| **Pivotal clinical field study:** The efficacy and safety of buprenorphine HCl extended release injectable solution for the control of post-operative pain associated with orthopaedic surgery, ovariohysterectomy, and castration in cats under clinical conditions. 2014. | |
|---|---|
| Objectives | Demonstration of efficacy and field safety of a buprenorphine HCl extended release sterile injectable solution for the control of post-operative pain in cats. |
| Study sites | Multi-centre (8 sites in U.S.) |
| Study design | randomised, placebo-controlled, masked |
| Compliance with regulatory guidelines | GCP |
| Interventions: Test product | Investigational veterinary product (IVP): final market formulation of 3 mg/ml buprenorphine HCl extended release sterile injectable solution (supplied in 10 ml glass vials). Dosage: 0.3 mg buprenorphine HCl per kg body weight. Control product (CP): commercially available formulation of physiologic saline (0.9% sodium chloride). IVP and CP were administered once at day 0 via subcutaneous injection in the interscapular space at a |
| Control product/ Placebo | |

| | |
|---|---|
| | volume equivalent to 0.1 ml/kg body weight, 30 minutes to 1 hour before the anticipated start of surgery (*i.e.* first incision). |
| Animals | 108 male and 140 female domestic cats, between 1.1 and 6.4 kg (mean of 3.3 kg) and aged from 3.8 months to 9 years. |
| Eligibility criteria | Clinically healthy cats presented to the clinic for a bilateral forelimb declaw (onychectomy) and reproductive sterilisation (ovariohysterectomy or castration). A baseline physical examination and blood sampling (haematology, coagulation profile and serum chemistry) were performed before inclusion. |
| Outcomes/endpoints | Primary efficacy endpoint: percentage of success at 24 hours with superiority established by a statistically significant difference between the treated and control groups. A case was considered a treatment success within an assessment period if it completed the period without requiring rescue. Animals that received rescue pain medication or were removed due to adverse events related to study treatment during the assessment period were considered treatment failures for that period and the remainder of the study. Secondary efficacy endpoints: recovery, behaviour observed from a distance, sedation, opioid excitation, behaviour during social interaction, response to palpation, and overall pain. Safety variables: body weights, laboratory analysis, abnormalities at physical examinations, incidence of adverse events. |
| Method | Surgical procedures: all cats (100%) received acepromazine (pre-medication) and lidocaine HCl (metacarpal four-point ring block on each forelimb). Isoflurane was used in 93.6% and 94.3% of the cats in the IVP and CP groups, respectively. Sevoflurane was used in the remaining cats (*i.e.* 6.4% and 5.7% in the IVP and CP groups, respectively). Propofol and fluids were used in about 80% of the cats and ketamine in about 20% of the cats. Diazepam, atropine sulphate and glycopyrrolate were used in 62, 16 and 1 cats, respectively. Procedures for declawing followed current standard of care guidelines (surgical scalpel, laser, or guillotine nail trimmers). Ovariohysterectomy was performed via a midline incision. Castrations were performed via a scrotal approach according to the current standard of care guidelines.<br><br>Post-surgical assessments: at day 0 the anaesthetic recovery was scored once after surgery from 0 (excellent) to 3 (poor). Then, 30 minutes after recovery (*i.e.* when the cat was awake, aware of surroundings and responsive) and at 2, 3, 5, 9, 24, 28, 32, 48, 52 and 56 hours post-extubation, cats were evaluated for behaviour at a distance, sedation/opioid excitation, behaviour during social interaction, response to palpation and overall pain assessment, using a scoring system. A physical examination was performed at 24, 48 and 72 hours |

| | |
|---|---|
| | post-extubation including a record of any abnormality noted in appetite, urine production and stool production. A blood sampling (haematology and serum chemistry) was performed at 72 hours post-extubation.<br><br>Injection site observations: upon injection by the unmasked treatment administrator; at 24, 48, and 72 hours post-extubation by masked study personnel. |
| ***Results*** | |
| Outcomes for endpoints | Overall treatment success at 24 hours was 39.7% in the CP group and 68.8% in the IVP group. It was 38.0% and 37.2% for CP and 65.6% and 64.8% for IVP at 48 hours and 72 hours, respectively. The difference between groups for the treatment success percentage at 24 hours was not statistically significant (p=0.1086). Of the 120 cases rescued (44 IVP, 76 CP), the highest percentage of rescues in both groups occurred within 30 minutes post-recovery (41% of the IVP cats and 42% of the CP cats). The majority (93%) of all rescues occurred by 24 hours following extubation. Eight more cases (5 IVP, 3 CP) were rescued thereafter. As rescue therapy, butorphanol tartrate was administered to 33 and 71 cats in the IVP and CP groups, respectively; meloxicam was given to 26 and 46 cats in the IVP and CP groups, respectively; robenacoxib was used in 18 and 30 cases from the IVP and CP groups, respectively. Dexmedetomidine was administered to 1 CP cat.<br><br>Secondary efficacy variables: only 3 parameters (behaviour during social interaction, response to palpation, and overall pain assessments) at the first timepoint post-extubation (within 30 minutes after recovery) had significantly lower values (i.e. improved pain scores) in the IVP group than the control group. |
| Adverse events | The most common adverse events occurring in at least 5% of all the cats in either treatment group were tachycardia, hypotension, hypothermia, hyperthermia, dysphoria, bradypnoea, immediate pain on injection and post-surgical bleeding from a digit. Frequencies of these events were similar between groups with the exception of hyperthermia which was higher in the IVP group (48.8% IVP; 17.1% CP), hypothermia which was higher in the CP group (33.6% IVP; 43.9% CP), and immediate pain on injection which was higher in the IVP group (11.2% IVP; 0.8% CP). Only hyperthermia was statistically significantly different between groups (p<0.0001). No statistical analysis was performed for the incidence of pain at injection. An injection site abnormality was present in only 1 cat (IVP group). It was a 2-3 cm area of alopecia noted at 48 and 72 hours. Injection site lumps were reported in 2 IVP cases 2 days after study exit. |

*Discussion:*

The primary endpoint was the treatment success percentage at 24 hours, with success being defined as the cat not requiring rescue pain medication or removal from the study due to adverse events. If success at 24 hours was statistically significant, success on Day 2 was evaluated. A cat was considered a success on Day 2 if it required no rescue between 0 and 48 hours. The same rules applied for assessment at Day 3 (0 to 72 hours). The applicant did not specify a value for the difference between the treatment group success percentages which could be considered clinically relevant. As for both pilot studies, it appears that the choice of the primary efficacy variable (percentage of success at 24 hours) was not adequate for the demonstration of efficacy of the product for the control of pain for 3 days.

Similarly to the dose determination and dose confirmation studies, the timing of the administration of Somnena (30 minutes to one hour before surgery) is questionable given that the pharmacokinetic studies indicated a $T_{max}$ of 12 to 60 hours.

Lack of pain control (failure to treatment) was stated if the cat received rescue pain medication or was removed due to an adverse event related to study treatment. Contrary to recommendations in recently validated pain scoring systems in cats, there was no specific score associated with the need for rescue. As was also the case for the dose confirmation studies, the subjective nature of the pain assessment in this study could have led to reduced ability to effectively discriminate between painful and non-painful cats. The results were 68.8%, 65.6% and 64.8% of treatment success (*i.e.* failure rate of 31.2%, 34.4% and 35.2%) in the group having received Somnena at 24, 48 and 72 hours, respectively. The effect of placebo was between 37.2 and 39.7% of treatment success. The observed difference between both groups for the primary endpoint was not statistically significant (p=0.1086). Therefore, treatment success was not statistically analysed for Days 2 and 3. Moreover, the results observed for the different success rates in the group treated with Somnena appeared very weak in comparison with other published results for the use of analgesic drugs for post-operative pain in cats or dogs.

The different variables (secondary criteria) assessed for pain evaluation were not sufficiently discriminatory between the two groups. The only significant differences were seen for 3 out of the 6 assessed parameters 30 minutes after recovery between the treated and placebo groups, and no more differences from 2 hours until study completion were observed for all the secondary criteria.

Furthermore, very few of the cats in the control group required rescue analgesia on days 2 and 3. This may have been related to e.g. the high number of cats that had already received rescue treatment on Day 1, lack of persistence of pain, or insufficiently sensitive pain evaluation. Regardless of the cause, this prevented evaluation of the analgesic effect of the product over the full 72 hour period of the claim.

The validity of the chosen model to investigate the efficacy of Somnena in pain relief for 3 days was therefore questionable. Indeed, no difference was seen between treatment with Somnena and placebo for the primary endpoint or for secondary variables at 2 hours post-extubation.

Opioids are recommended as analgesic drugs in cases of moderate to severe pain. At the time if withdrawal of the application the applicant had been questioned on the adequacy of the model employed for the pivotal field study for the demonstration of the efficacy of the product. In particular the models of onychectomy+castration *versus* onychectomy+ovariohysterectomy would have needed to have been compared in terms of level of pain, and if relevant, separate results should have been given for both surgical procedures.

Onychectomy is not permitted as routine surgery in the EU (see also below), and the results of this study and the dose confirmation studies can therefore not easily be extrapolated to surgical cases in the EU.

Further evidence of the product's efficacy in a wider range of surgical cases relevant to use in the EU would therefore have needed to be provided.

In summary, a significant treatment benefit had not been demonstrated at any time point over the period of time that the product was intended to be effective. There were problems with the design of this field trial which would have needed further clarification. Further clinical data would have been required to demonstrate a treatment benefit over a three day period in surgical cases representative of EU practice. However, further consideration was required regarding the dose and time to onset of effect before any such studies were conducted.

Among the adverse events cited with the use of buprenorphine, post-anaesthetic hyperthermia (39.4 °C) and pain at injection were both significantly more frequently reported in the Somnena group than in the control group, with 48.0% and 11.2% of the cats concerned, respectively.

**Choice of the model of pain through clinical studies:**

For all the submitted efficacy studies, the chosen model of pain using routine onychectomy in cats raised ethical concerns with regard to animal welfare. Furthermore, according to the CVMP Guideline on the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (NSAIDs; CVMP/EWP/1061/2001) and VICH GL9 (Good Clinical Practice), whatever procedure is used in clinical studies should be practiced and ethically acceptable in the EU.

## *Overall conclusion on efficacy*

*Pharmacodynamics:*

The mode of action of buprenorphine, the active substance in the product Somnena, is well documented. One behavioural study in cats was provided with a non-final formulation, which showed some alteration in temperament, mydriasis and pupillary light reflex (PLR) and pain.

*Pharmacokinetics:*

The pharmacokinetic characteristics of buprenorphine after administration of buprenorphine HCl formulated in co-polymer matrices in cats were documented in three non-GLP studies. Buprenorphine plasma concentrations rose slowly after administration. In the two studies which used doses of the RTD of 0.3 mg/kg, plasma buprenorphine concentrations reached 1.0 ng/ml in 100% of the cats within 24 hours of administration and remained above 1 ng/ml until 72 hours after administration. $C_{max}$ values ranged from 1.33 to 5.35 ng/ml. However, not all pharmacokinetic parameters were provided.

*Dose determination:*

The applicant considered that a buprenorphine plasma concentration of 1 ng/ml was generally considered analgesic in humans, rat and mice. However, no study using a model of induced pain had been used to establish the threshold for pain control in cats.

The proposed therapeutic scheme for the control of post-operative pain in cats for 3 days was not validated by PK/PD analysis, and was therefore difficult to establish because of the individual variability of cats, and the absence of correlation between plasma buprenorphine concentrations and analgesia. The proposed dosing regimen was therefore not considered to be adequately demonstrated and, at the time of withdrawal of the application, questions had been asked in order to attempt to resolve this.

*Tolerance:*

In a number of TAS studies (pivotal and supportive), Somnena induced pain on injection reflected by bilateral mydriasis and reactions at injection sites (erythema, swelling, discharge). The frequency,

severity and persistence of these lesions increased with increasing the dose. The studies indicated no interactions between an extended release buprenorphine hydrochloride and concomitantly used butorphanol.

Follow-up assessment of tolerance during pre-clinical and clinical studies confirmed that the product induced bilateral mydriasis and pain on injection. Respiratory depression, alopecia and lumps at the injection site were also reported.

At the time of withdrawal of the application it was not possible to conclude on the tolerance of the product when used as proposed.

*Efficacy:*

One laboratory dose determination study, 3 (pilot) dose confirmation studies and 1 pivotal field study were provided to justify the dose rate and to confirm the efficacy of the product. The chosen model of pain for all efficacy studies was onychectomy, either alone or combined with other surgical procedures (ovariohysterectomy or castration).

However, the use of onychectomy as a pain model does not appropriately reflect the variety of surgical cases presented in Europe. In addition, the CVMP expressed ethical concerns about this choice of model and considered that further data, using a more appropriate model would be needed to support the efficacy.

Due to several concerns of over the design and conduct of the dose determination study, it was considered that the evidence to support the superiority of 0.3 mg/kg over the other doses to be weak.

Furthermore, the selected dosing regimen came further into question-based on the inconclusive results seen in the dose confirmation and field studies.

It should also be highlighted that the 3 dose confirmation studies including the 2 pilot dose confirmation studies conducted under field conditions at the recommended dosage were insufficiently documented, and deficiencies in the study design and presentation of results did not allow conclusions on the recommended therapeutic dose at the time of withdrawal.

Finally, no difference with a placebo was seen for both the primary and secondary criteria in the pivotal field study. This field study could only be considered as supportive data. The model of pain chosen for the two pilot dose confirmation studies at the recommended dosage and the pivotal field trial was the same, i.e. onychectomy under lidocaine ring block + ovariohysterectomy or castration.

At the time of withdrawal of the application, in the absence of clinical data demonstrating the efficacy of Somnena for the control of post-operative pain for 3 days following surgery in cases that were representative of ethically acceptable surgical cases in the EU, only very limited conclusions could be made regarding the benefit of Somnena 3 mg/ml solution for injection in cats when used as proposed.

# Part 5 – Benefit-risk assessment

## *Introduction*

Somnena is a prolonged-release non-aqueous solution for injection containing 3 mg/ml buprenorphine (as the hydrochloride) presented in multidose vials. The product is a long-acting opioid analgesic which was intended to be used in cats for the control of post-operative pain for up to 3 days, following a single subcutaneous dose of 0.3 ml/kg bw.

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

application).

## Benefit assessment

## Direct therapeutic benefit

A number of pre-clinical and clinical studies were provided, all using Somnena (or a similar near-final formulation) in comparison to placebo for onychectomy (declawing) in cats, either as a model under laboratory conditions or as routine surgery combined with ovariohysterectomy or castration under field conditions.

Efficacy of the proposed dose was not demonstrated by the results of either the pre-clinical or the clinical studies. No difference was seen between placebo and test product treatment groups for both primary and secondary criteria during the pivotal clinical study. A number of questions on the studies remained to be addressed at the time of withdrawal of the application. The CVMP considered that new clinical data would be necessary to demonstrate the efficacy of Somnena for pain control for 3 days, and that these data should be obtained in a setting more representative and ethically acceptable in Europe than onychectomy (declawing). At the time of the withdrawal of the application and in the absence of such data, only very limited conclusions could be made regarding the benefit of Somnena 3 mg/ml solution for injection in cats when used as proposed.

At the time of the withdrawal of the application, the clinical benefit of the product was not considered to have been demonstrated.

## Additional benefits

Somnena might have had an additional benefit in comparison to immediate release products because of its prolonged-release formulation.

## Risk assessment

*Quality:*

At the time of withdrawal of the application, major questions had been raised regarding the development, manufacture and control of both the active substance and the finished product.

*Safety:*

*Risks for the target animal:*

At the time of withdrawal of the application, questions had been raised regarding local reactions and the potential for the development of fibrosarcomas in cats following the use of the product.

*Risk for the user:*

At the time of application's withdrawal a new risk characterisation was considered to be required, and no final conclusions on user safety could, therefore, be reached until those issues were satisfactorily addressed.

*Risk for the environment:*

The product was not expected to pose a risk for the environment when used according to the proposed SPC.

## Risk management or mitigation measures

The identification of necessary risk management or mitigation measures remains outstanding due to the inconclusive assessment.

## *Evaluation of the benefit-risk balance*

At the time of the application's withdrawal concerns had been raised regarding the quality and safety of the product, and in the light of the major concerns on the dosing regimen and efficacy, the clinical benefit of the product was not considered to have been demonstrated.

In the presence of outstanding major and other concerns, the benefit-risk balance of the application was therefore inconclusive.

## *Conclusion*

Based on the original data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that Somnena was not approvable since "major objections" had been identified which precluded a recommendation for a marketing authorisation. The details of these major objections were outlined in a list of questions. At the time of withdrawal of the application, responses to the questions remained pending.

No conclusions could be therefore taken on the benefit-risk balance of the application.