EPAR type II variation for Suprelorin

International Non-proprietary Name: deslorelin acetate

Procedure No. EMEA/V/C/109/II/007

EU/2/07/072/003-004

Scope of the variation:

C.II.1 - Variations concerning a change to or addition of a non-food producing target species

This variation concerns the addition of male ferrets as target species for the 9.4 mg Suprelorin implant.
Background information on the variation

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No. 1234/2008, the marketing authorisation holder, Virbac S.A., submitted to the European Medicines Agency (the Agency) on 20 December 2010 an application for a Type II variation for Suprelorin.

1.1.1. Scope of the variation

<table>
<thead>
<tr>
<th>Previous</th>
<th>Proposed</th>
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<tbody>
<tr>
<td>Currently only authorised for use in dogs at strengths of 4.7 and 9.4 mg.</td>
<td>Addition of male ferrets as a target species for the 9.4 mg Suprelorin implant.</td>
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</table>

2. Scientific discussion

Introduction

Suprelorin 9.4 mg was authorised in the EU as a line extension to Suprelorin 4.7 mg on 01 July 2010 indicated for the induction of temporary infertility in healthy, entire, sexually mature male dogs with duration of efficacy of up to at least 12 months. The subject of this Type II variation application is the addition of male ferrets, to the existing marketing authorisation for Suprelorin 9.4 mg. The active ingredient is deslorelin, a nonapeptide analogue of gonadotropin releasing hormone (GnRH).

MUMS classification

The application has been submitted in accordance with Minor Use Minor Species (MUMS) requirements (cf. Guideline on Efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/EWP/117899/2004)). In February 2010 the Committee for Medicinal Products for Veterinary use (CVMP) discussed the request for MUMS/limited markets classification for Suprelorin 4.7 mg for ferrets and agreed to classify the product as MUMS since ferrets are a minor species and the indication was considered a minor use. While the original MUMS request concerned Suprelorin 4.7 mg for ferrets, the subject of this application is Suprelorin 9.4 mg implant, an identical formulation to Suprelorin for dogs.

The medicinal product is intended as an alternative treatment to surgical castration to control skin odour and intraspecies aggressive behaviour in ferrets. There is increasing evidence that surgical castration may precipitate the development of hyperadrenocorticism due to an increased secretion of gonadotropins (LH and FSH). Suprelorin containing the active substance deslorelin is a depot GnRH implant which acts by long inhibition of the production and release of LH and FSH due to a desensitisation of gonadotropin receptors in the pituitary gland. Consequently, it is considered an alternative to surgical neutering and thereby limiting the development of hyperadrenocorticism in ferrets.

Safety

No significant new safety data were provided in the dossier. The applicant did not present a specific target animal safety study in the ferret, but referred to the data presented for Suprelorin 9.4 mg in the dog, including pharmacovigilance data from dogs. In addition clinical safety data were available from a clinical study conducted with Suprelorin 9.4 mg in male ferrets.
The data from dogs demonstrated that Suprelorin 9.4 mg was well tolerated, also after long-term use (two or three consecutive implantations). This was confirmed by the considerable overdose of deslorelin (6-fold) used in the pivotal target animal safety study as well as the pharmacovigilance data presented covering a period of two years.

In the clinical study conducted with Suprelorin 9.4 mg in ferrets, no treatment related adverse reactions were reported during the study and hence no adverse reactions were included in the SPC section 4.6. Section 4.10 (Overdose) informs that no data are available in ferrets.

Considering the MUMS requirements and since the pharmacological and toxicological properties of deslorelin in ferrets are not expected to be significantly different from those in dogs, the absence of an ADME study in ferrets was justified. Thus the absence of any pharmacokinetic information in the SPC section 5.2 was justified. As also for Suprelorin 9.4 mg for dogs, the pharmacological actions of deslorelin in ferrets are more relevant than its pharmacokinetic properties. Moreover, plasma deslorelin seems to be difficult to assay accurately, due to low concentrations detected in plasma attributed to the slow release of deslorelin from the implant.

No treatment related adverse events were observed in an ongoing multi-centre open clinical GCP study.

A user safety risk assessment conducted in accordance with CVMP guideline on the User Safety for Pharmaceutical Veterinary Medicinal Products (EMEA/CVMP/543/03) was provided. The risk assessment for the user when treating a ferret is the same as when treating a dog. The addition of ferrets as target species was not expected to cause additional risks for the user compared to the risks when handling/treating dogs. The risk is further mitigated by the recommendation to administer the implant under general anaesthesia, which reduces the risk of sudden movements hence reducing the risk of accidental self injection. The user safety warnings in the SPC remain therefore unaltered.

A Phase I Environmental Impact Assessment has been provided in accordance with the appropriate guideline (VICH GL6). Since Suprelorin 9.4 mg is indicated for non-food producing animals only, the environmental exposure is minimal. Further assessment is therefore not necessary and the environmental assessment stops at Phase I.

**Efficacy**

As this application concerned an authorisation for use in a minor species, no preclinical data in the target species was needed and reference could be made to the data presented for the dog in the original dossier. According to the MUMS guideline EMEA/CVMP/EWP/117899/2004 this is acceptable when the product is already authorised for the same indication in a major species in which pharmacology is likely to be comparable.

No dose determination study was provided in ferrets. This is acceptable in accordance with the MUMS guideline as the efficacy of the product at the recommended dose regime is demonstrated in an adequate and controlled dose confirmation study in the target species. Further, it is acknowledged that dosages in ferrets are normally determined empirically based on the practical knowledge of use of the product in other species, in particular the dog.

As a pivotal study a one-centre open randomised double-controlled clinical non-GCP study of parallel-group design was presented. The objective was to investigate the effect of treatment with Suprelorin 9.4 mg using the primary end points plasma FSH and testosterone concentrations, testis size and spermatogenesis of intact male ferrets. 21 healthy, adult intact male ferrets at the beginning of the breeding season, bodyweight 1.0-1.7 kg, age 1-2 years, were placed in three treatment groups, each containing seven ferrets – one negative control group implanted with placebo implant, one treatment group implanted with deslorelin implant 9.4 mg and one positive control group with animals surgically castrated on day 0.
The study was initiated at the beginning of the breeding season, thus the plasma testosterone concentrations were low in all treatment groups at D0. Gonadal activity is seasonal both in male and female ferrets and more than 12 hours of day light are crucial in the promotion of reproductive activity. The length of the breeding season therefore depends on the weather and geographical location. For this study it was expected to start in March and end in September.

In male intact ferrets, testis size is correlated with testosterone concentrations and this has been supported by findings in recent studies and data available in the published literature. Testosterone concentrations in ferrets are variable and even during the breeding season some animals can be expected to present low values (e.g. 0.2 ng/ml). At this stage, an established threshold value for infertility regarding testosterone concentration in the ferret has not been reported. However, the data reviewed show that surgically castrated ferrets as well as intact male ferrets that have been treated with the deslorelin implant present testosterone levels which are either below the limit of detection (0.05 nmol/L) or well below 0.1 ng/ml.

The duration of effect was only studied until week 68 post treatment. The study shows that the level of testosterone in the deslorelin implant group was as low as for the surgically castrated group (no significant difference between surgically castrated and deslorelin implant groups) and significantly lower in comparison to the placebo group. Even though the number of ferrets had decreased in both placebo (n = 5) and surgically castrated (n = 6) groups, testosterone concentrations found in each of these groups, placebo (sexually active) and surgically castrated (sexually inactive) are representative of their sexual status, therefore it is considered that they were satisfactory for comparison with the implant treated group.

In addition, a letter by the principal investigator in the pivotal study reporting on experience of use of the product was provided to support the justification for clinical efficacy. Different Suprelorin implants available for use in dogs containing 4.7 mg and 9.4 mg deslorelin had been used in 113 privately owned ferrets (58 male and 55 female). Although this information is yet to be published, in 2010 the investigator initiated a survey among the owners of the ferrets that had been administered the 4.7 mg deslorelin implant two years before. The survey indicates duration of effect evaluated by the owners based on odour of the ferrets or increase in testis size in male ferrets with the 4.7 mg implant between 1 and 3 years. The investigator also reports that duration of effect was increased in ferrets implanted with the 9.4 mg deslorelin implant in comparison to the 4.7 mg according to the owner’s observation and that based on the data available in dogs the duration of the 9.4 mg implant is likely to be twice as long as that reported for the 4.7 mg implant.

The onset of effect was evaluated in the pivotal study, showing a complete onset of effect at week 5 after implant placement. Although testosterone levels were significantly lower in the deslorelin implant group in comparison to the placebo at week 4 after implantation, a significant difference in testicle size between the implant and the placebo group was not observed until week 5 after treatment. Therefore, this provides a more comprehensive indication of effect evaluating both testosterone concentrations and testis size. Duration of effect has been demonstrated for at least 68 weeks (16 months) after application of the implant with no significant difference between the implant and surgically castrated groups, however a significant difference between the implant and placebo group. However, further investigations indicate that the duration of effect of the 9.4 mg implant could be considerably longer. In view of the above, termination of effect may be demonstrated by increase in testis size in male ferrets with the corresponding increase in blood testosterone concentrations.

Regarding the above, the wording of the SPC has been modified as follows:

Section 4.4 Special warnings (ferrets)

"Ferrets"
Infertility (suppression of spermatogenesis, reduced testis size, levels of testosterone below 0.1 ng/ml, and suppression of musky odour) is achieved from 5 weeks up to 14 weeks after initial treatment under laboratory conditions. Treated ferrets should therefore still be kept away from jills on heat within the first five weeks after initial treatment.

Levels of testosterone remain below 0.1 ng/ml for up to 16 months. Not all parameters of sexual activity have been tested specifically (seborrhoea, urine marking and aggressiveness). Any mating that occurs more than 16 months after the administration of the product may result in pregnancy.

The need for subsequent implantations should be based on the increase in testis size and/or increase in plasma testosterone concentrations and return to sexual activity.

The reversibility of effects and ability of treated hobs to produce offspring subsequently has not been investigated. Therefore, the use of Suprelorin should be subject to a benefit-risk assessment performed by the responsible veterinarian.

In certain cases, the implant may be lost from a treated ferret. If loss of the implant is suspected in connection with the first implantation, this can be confirmed by observing no reduction in testis size or plasma testosterone levels as both should reduce under correct implantation. If loss of the implant is suspected following re-implantation, a progressive increase will be seen in testis size and/or plasma testosterone levels. In both of these circumstances a replacement implant should be administered.

The applicant submitted three published papers and data from one ongoing corroborative study to further support efficacy and the claims for ferrets in the proposed SPC. The Suprelorin implants with 4.7 mg and 9.4 mg had the same pharmacodynamic and pharmacokinetic properties in dogs, and the release profiles were qualitatively very similar, but quantitatively the daily release of deslorelin was greater from the 9.4 mg implant in dogs leading to twice the duration of effect for the high dose implant (6 months for 4.7 mg versus 12 months for 9.4 mg). As the mechanism of action is very general across animal species for Suprelorin (a GnRH agonist) it is accepted that the data obtained with 4.7 mg deslorelin implant in ferrets in the corroborative study can present support to the data from the pivotal study with the 9.4 mg deslorelin implant in ferrets. The new data represents a worst case situation for the product with expected shorter duration of effect than for the high dose implant.

The applicant provided further support in order to establish a clinically relevant testosterone threshold value for infertility in ferrets. The ongoing corroborative open multi-centre field GCP study is conducted to evaluate the clinical efficacy of a 4.7 mg deslorelin implant on reversible long term contraception in 29 young intact male ferrets in rut. Levels of testosterone below 0.1 ng/ml have been shown to correlate to inhibition of sexual behaviour in the ferrets, therefore this threshold seems relevant to demonstrate sufficient clinical effect of the Suprelorin implant.

It is acknowledged that there is a natural variance in the circulating levels of testosterone in ferrets both due to episodic fluctuation caused by the pulsatile release from the testis and due to the fact that these animals have only one annual reproductive cycle. The natural variance in testosterone levels is present in the individual ferret during the reproduction cycle as well as between animals at the same time point of the cycle. Results from the ongoing field study bring support to the onset of infertility from 5 weeks. Duration of effect cannot yet be supported from this study as data are still awaited from the end of the first breeding season, middle of the second breeding season and return to sexual activity after treatment (data from clinical examinations and blood samples for plasma testosterone analysis). The duration of effect is correctly confirmed as demonstrated in the pivotal study to be at least 68 weeks (16 months), and there are indications that the yet to be confirmed duration of effect for the 9.4 mg implant could be considerably longer. A recommendation was included in the SPC for using tissue glue and explaining how a loss of the implant could be observed by the owner and which actions should be followed afterwards.
The SPC Sections 4.4, 4.5, 4.6 and 4.9 and the related in the leaflet have been amended accordingly including the necessary changes.

3. **Benefit-risk assessment**

The benefit-risk balance is positive for Suprelorin 9.4 mg implant for ferrets taking into account the data provided and in addition it offers an alternative treatment to surgical castration for induction of infertility in ferrets.

4. **Overall Conclusions of the evaluation and recommendations**

This variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

The CVMP also reset the PSUR cycle for Suprelorin to enter a 6-monthly submission frequency.

5. **Changes to the community marketing authorisation**

Changes are required in the Annex I and III of the marketing authorisation.