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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

Withdrawal assessment report for a type II variation for Sileo (EMEA/V/C/003764/II/0022)

International non-proprietary name: dexmedetomidine hydrochloride

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

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Orion Corporation (the applicant), submitted to the European Medicines Agency (the Agency) on 22 December 2021 an application for a type II variation for Sileo.

On 30 August 2022, the applicant withdrew the application. In its letter notifying the Agency of the withdrawal of application, the applicant states that "the reason for withdrawal is based on a commercial decision."

1.2. Scope of the variation

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The variation is to modify the approved indication to include "Alleviation of anxiety and fear associated with owner departure".

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 3 and Part 4

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

The product Sileo 0.1 mg/ml oromucosal gel for dogs contains the active substance dexmedetomidine (dexmedetomidine hydrochloride 0.1 mg/ml), a selective alpha-2 adrenoreceptor agonist. Sileo is currently indicated for "Alleviation of acute anxiety and fear associated with noise in dogs". The proposed variation was to extend the approved indication to include "Alleviation of anxiety and fear associated with owner departure". In support of the proposed additional indication the applicant conducted one EU field trial to investigate efficacy and safety of 2-weeks treatment in client owned dogs with separation anxiety. In addition, an updated user risk assessment was provided as well as two expert reports: one on safety and one on efficacy.

2.1. User safety

The applicant submitted an updated User Risk Assessment according to the Guideline on User safety for Pharmaceutical Veterinary Medicinal Products (EMA/CVMP/543/03-Rev.1). No new risks were identified and no change to the wording in the SPC section 4.5 "Special precautions to be taken by the person administering the veterinary medicinal product to animals" has been proposed. This was accepted on the grounds that the amount of product that the user will have in their possession, the dose rate and method of administration were not expected to change as a result of the proposed indication.

2.2. Efficacy and target animal safety

The recommended dose (125 µg/m^2) for the proposed indication was the same as currently authorised for alleviation of acute anxiety and fear associated with noise. However, for the newly proposed indication, although the re-treatment interval of 2 hours was the same as for the existing indication, the maximum number of doses was two per day. It was accepted that the proposed dose and proposed treatment interval were justified, based on the clinical data submitted in support of the original application for market authorisation and that use of this dose regimen for the added indication was evaluated in the pivotal clinical study presented in support of the present variation application.

The applicant also proposed a maximum duration of treatment of 9 consecutive days. However, no specific target animal safety study was conducted in the context of this variation, and it was questioned if safe use over 9 consecutive days is sufficiently supported by the submitted 2-week field study (see further below). In the absence of support from a target animal safety study, the applicant was asked to further justify the prolonged treatment duration. Furthermore, the applicant was asked to provide justification for the efficacy of a 9-day treatment period, seeing as the condition intended to be treated is chronic in nature and typically requires other interventions such as behavioural therapy to be successfully managed.

Field study

The field study submitted in support of this variation application was conducted to evaluate the safety and efficacy of Sileo, compared to placebo for the alleviation of acute anxiety and fear associated with owner departure in client own dogs. This was a GCP-compliant, multicentric, randomised, double-blinded and placebo-controlled study. The study included 90 dogs enrolled at 15 different centres in Finland, Poland, the Netherlands, and Germany. To be included in the study, the dogs should, based on behaviour history and baseline video recordings, have experienced at least one of the following signs of owner departure related acute anxiety: destructive behaviour, restlessness/pacing or vocalisation. Otherwise, included dogs should be healthy (ASA status I or II), have normal cognition, be house-trained, and subjected to at least 5 separation anxiety related departures per week. Dogs undergoing medical or non-medical treatment (including behavioural training) for anxiety-related problems were excluded from the study.

Eighty-nine animals received treatment, 45 with placebo and 44 with Sileo (125 µg/m^2). Study treatments were given to the dogs at home by the dog owner as needed up to 2 times a day with a 2 h minimum interval for 2 weeks (at least once a day 5-7 times a week). On the first treatment day the treatment could only be given once, and the dog was not to be left alone. On other treatment days, study treatment was given to the dog 45-60 minutes before the owner left the dog. Evaluation of efficacy was performed by the dog owner based on video recordings of the dog's behaviour during the first hour after owner separation.

The primary endpoint for efficacy evaluation was owner assessment of the effect of study treatment on acute anxiety related to owner departure compared to usual behaviour of the dog when left alone before the study. The owner scored the effect as 1- excellent effect (the dog did not show signs of acute anxiety related to owner departure at all), 2- good effect (the dog's signs of acute anxiety related to owner

departure were infrequent/mild and the dog was able to calm down), 3- some effect (the dog showed somewhat less frequent/milder signs of acute anxiety related to owner departure but it was not able to calm down), 4- no effect (there was no reduction/change in the dog's signs of acute anxiety related to owner departure), or 5- worse (the dog's signs of acute anxiety related to owner departure were more frequent/stronger than before). The owner made the assessments on 5–7 days a week during the 2-week treatment period. If the dog was left more than once a day, assessment was only made for the first separation. Assessments were compared statistically between groups using a generalised linear model with treatment as an explanatory variable, and week and centre as covariates (the model also included × treatment interaction terms).

The secondary endpoint was owner assessment of individual signs of acute anxiety associated with owner separation: vocalisation, restlessness/pacing, destructive/rearranging behaviour, salivating, panting, licking/self-grooming, freezing/reduced motor activity, and other behaviour (to be specified by the owner). The occurrence of each sign was scored "none"=0, "only a few times"=1, "half of the time"=2, "most of the time"=3, "continuously"=4. In addition, the occurrence of urination and defecation was recorded as "no"=0 and "yes"=1. The owner made the assessments 2 days prior to the treatment period (baseline), on 5–7 days a week during the 2-week treatment period and at 2 days post-treatment. For statistical analysis, summary scores were created (by adding the scores of the signs of acute anxiety assessed by the owner for each day) and compared using a model with treatment as an explanatory variable, and week, centre and average of baseline summary scores as covariates (the model also included × treatment interaction terms). In addition, incidence of improvement was calculated for daily sum scores and for the predefined individual acute anxiety behaviour signs and was compared between the treatment groups. Improvement was declared when the average sum score on treatment or post-treatment was at least 30% lower than that at baseline. For individual signs, 20% lower than baseline was used.

Additional variables included "caregiver burden" (questionnaire on the dog owner's quality of life and rating of the global impression of level of burden of separation anxiety before and after the treatment period) and usability of the product.

Evaluation of safety included registration of adverse events, assessment of alertness, physical examination, bodyweight, cardiorespiratory status, and laboratory safety variables. Alertness was evaluated by the owner as "observational alertness" and "functional alertness" based on predefined scales (score 1-4). Both variables were evaluated 2 days during the baseline period and on treatment days 1 and 2 at 45–60 minutes after study treatment administration.

Seventeen dogs discontinued their participation in the study, 6 dogs in the test group (1 before treatment was started) and 11 in the control group. The most common reason for discontinuation was lack of efficacy reported for 4 dogs in the test group and 5 in the control group. Safety and efficacy evaluation was based on the full analysis set (FAS) which included data from all enrolled dogs which received at least 1 dose of the study treatment (n=89). For efficacy, analysis was also performed on a per protocol (PP) dataset which included dogs without significant protocol deviations (n=82).

Dogs in the two treatment groups were accepted as being comparable in terms of demographics.

Prior to start of the study, 44 dogs (22 in the test and control group, respectively) had been treated for anxiety. The majority of these treatments (87%) were non-medical treatments. Anxiety treatment with medical products were reported in 4 dogs (9.1%) in the test group and 6 dogs (13.3%) in the placebo group.

A median of 12 doses of Sileo (mean dose 124.5 µg/m^2) was administered to 44 dogs and placebo to 45 dogs during the study. The majority of the dogs in both groups received only one dose per day: 63.6% in the test group and 71.1% in the control group. In the test group, the mean number of treated study days was 11.3 (SD 2.45) and in the control group 10.6 (SD 3.28).

Efficacy

Excellent or good treatment effect was reported by 13.3% and 32.4% of the owners of dogs in the test group compared to 4.7% and 21.3% of those in the control group. A statistically significantly better treatment effect was reported by owners for dogs that had received Sileo compared to placebo when considering odds ratio for effect (OR 2.16; 95% CI 1.22–3.83; p=0.0086). The data was also analysed for the PP population and the results supported the primary analysis. The results in the control group indicating a notable "placebo effect" are not unexpected considering the subjective nature of the primary endpoint. Week (p=0.4372) and treatment × week (p=0.5287) interactions were not statistically significant in the model. In contrast, a statistically significant centre effect was seen (p< 0.0001) which was suspected to be as a result of the small centre sample sizes (out of the total 15 centres, there were 6 centres with only 1 dog randomised).

Subgroup and sensitivity analyses of the primary variable were provided. No subgroup main effects or subgroup × treatment interaction effects were statistically significant, and the treatment effect remained statistically significant in all analyses except for the subgroup analysis adjusting for previous use of medical (prescription) treatment for anxiety. Considering that only 10 included dogs had a history of previous medical treatment of anxiety (4 in the test group and 6 in placebo), the sample size was considered too limited to draw conclusions on larger/smaller treatment effects in specific subgroups.

The primary analysis of the secondary endpoint using average weekly summary scores showed no significant treatment effect (difference of means [test vs control]: -5.58; 95% CI -12.02, 0.86; p=0.0883). The results were similar in the FAS and PP-population. When individual signs were analysed, a statistically significantly greater decrease from baseline in weekly averages was seen in "panting" for dogs in the treated group when compared to dogs in the control group (difference of means [test vs control]: -0.313; SD 0.142, p=0.0307). The result from the PP-population supported this and in addition, a statistically significant greater decrease from baseline in weekly averages was also seen for "destructive/rearranging behaviour" (difference of means [test vs control]: 0.2181; SD 0.1087; p=0.0489). There was no statistically significant difference between the groups for improvement of sum scores on treatment (54.5% dogs classified as improved in the test group compared to 42.2% in the control group, p=0.2917). There was also no statistically significant difference between the groups for improvement in individual signs. However, numerically higher percentages of dogs in the treated group had improvement on treatment for destructive/rearranging behaviour (59.1% vs 37.8%, p=0.0571) panting (54.5% vs 46.7%; p=0.5272), restlessness/pacing (68.2% vs 57.8%; p=0.3818), salivating (18.2% vs. 11.1%; p=0.3837), and vocalisation (61.4% vs. 48.9%; p=0.2888).

No statistically significant improvement in the dog owner's quality of life was seen for any of the questions after the 2-week treatment period. There was also no statistically significant improvement in the dog owners' global impression of level of burden of separation anxiety after 2 weeks treatment (improvement was seen in 32.5% of the dogs in the Dexmedetomidine treated group compared to 27.5% of the dogs in the placebo group, p=0.8329). At the end-of-study visit, the majority of the dog owners assessed the usability of the product as very easy (53.7%) or easy (30.5%). One owner (1.2%) assessed the use as very difficult.

In principle, the use of owner assessments of treatment efficacy can be accepted as it is acknowledged that dog owners are familiar with and able to recognise signs of acute anxiety in their dogs. However, given that the parameter by itself is considered to be lacking in clinical specificity (no specific measurable scale used) it was difficult to estimate the clinical relevance (e.g., the actual clinical improvement of the dogs) based only on the primary endpoint, and the absence of an effect having been demonstrated for the secondary efficacy endpoint (owner departure related signs of acute anxiety) was considered a major concern. In addition, no statistically significant differences were reported for the additional variable "caregiver burden" when comparing treatment and placebo groups.

Combined with the above, the failure to demonstrate a statistically significant and clinically meaningful effect for the secondary efficacy parameter (owner departure related signs of acute anxiety) and also noting the findings in respect of the additional parameter "caregiver burden" raised serious concerns in terms of the adequacy of the efficacy data package provided Further justification that a clinically relevant effect has been demonstrated needed to be provided and therefore the applicant was asked to further justify how the efficacy data provided may be considered adequate to support the proposed indication.

Another concern on efficacy was that it needed to be clarified if the study population can be considered representative for the entire range of clinical signs (mild-moderate-severe) associated with separation anxiety. The applicant stated that an explanation for the lack of statistically significant results for the secondary endpoint could be that, except for panting, the other specific signs of acute anxiety were less commonly reported at baseline which may indicate that predominantly dogs with mild signs of separation anxiety were included in the study. The applicant was also asked to clarify if the diagnosis of separation anxiety was set by a veterinarian/behavioural specialist and to discuss the severity of clinical signs in the included dogs.

Of note was the fact that efficacy was only evaluated during the first hour of owner separation, which is information that was not proposed to be reflected by the SPC. Extrapolation of results from the first hour to the entire separation period was not considered sufficiently justified. The applicant was asked to address this further, taking into account the expected treatment duration of Sileo and the status of the dog in terms of anxiety levels and associated behaviour when the effect of treatment ceases and the owner is still absent.

It was also noted that the product is intended for administration 45-60 minutes prior to owner separation. The currently approved SPC indicates that the product is only to be administered when the dog shows first signs of anxiety or when the owner detects a stimulus (noise). No specific justification for the proposed timing of treatment administration in advance of separation has been provided. As maximum plasma concentration of dexmedetomidine occurs at approximately 0.6 hours after oromucosal administration (according to SPC section 5.2) it was questioned whether the different approach to timing of administration (in anticipation of a stressor event) being proposed for anxiety associated with owner departure (compared to that associated with noise) is optimal, as anxiolytic effects may be waning by the time the owner departs. Indeed, according to published literature cited by the applicant, maximum level of departure-related anxious activity has been reported to occur during the first hour after the owners' departure.

Furthermore, given that the newly proposed indication was similar to the currently authorised one, the proposal to recommend treatment in advance of the stressor event, and not at time of event, appears to be inconsistent between the indications and has the potential to result in confusion for the owner and/or prescriber.

Therefore, applicant was asked to further justify the proposed timing of product administration in respect of owner departure and to propose clear instructions on dosing in the SPC for the different indications.

A number of additional, specific points also needed to be further addressed.

Target animal safety

There were no reported serious adverse events (AE). In the test group 22 adverse events in 10 dogs (22.7%) were reported; compared to 11 AEs in 8 dogs (17.8%) in the control group. Also, more AEs were classified as moderate in the test group (12 out of 22 events) compared to (1 out of 11 events) in the control group. Nine AEs in 6 dogs (13.6%) in the test group were assessed as related to study treatment by the applicant (possible or probable causality). These were anxiety (n=2), pruritus (n=2), increased blood urea nitrogen or creatinine (n=1), urinary incontinence (n=1), hallucination (n=1), elevated liver

enzymes (n=1), and elevated symmetrical dimethylarginine (n=1). In addition, 1 AE of somnolence leading to dose reduction was reported. The applicant was asked to provide explanations for the reported adverse events to allow for causality assessment and to amend section 4.6 of the SPC to include adverse events currently not covered.

No significant differences in the cardiorespiratory status were seen between groups at the end of the study.

There were several laboratory safety variables outside the reference ranges. Most of these were considered as not clinically relevant by the applicant.

The assessment of alertness showed that more dogs in the test group were sleeping during the first two treatment days. On treatment day one, 12 dogs in the test group (27.9%) were sleeping compared to 8 dogs in the control group (17.8%). On treatment day two, 5 dogs in the test group (11.9%) were sleeping compared to 2 dogs in the control group (4.5%). On treatment day one there were 8 dogs (18.6%) in the treated group and 6 dogs (13.3%) in control group that were slow to stand up. One dog in the test group was reluctant to stand up, hesitated to move/was uncoordinated when walking, and slow to respond to call and not as alert as usual. This dog was mistakenly administered 187 µg/m^2 instead of (125 µg/m^2 on the first day. At day two, 7 dogs (16.7%) in the test group and 3 (6.8%) in the control group were slow to stand up but could walk normally.

To summarise, the use of Sileo for separation anxiety would result in two consequences for target animal safety: a prolonged treatment duration of 9 days, and the dog will be left alone after treatment has been administered. Consequently, the applicant was asked to justify the safe use during 9 consecutive days; given that this is only supported by data from the 2-week field trial and that it is unclear from exposure data how many dogs were treated for ≥9 consecutive days.

To mitigate risks associated with leaving the dog after administration of the product, the applicant proposed that a test dose should be given, and the dog should be observed for 2 hours to make sure the selected dose of the product is not associated with adverse reactions and that it is safe for the treated dog to be left alone. The approach of a test dose was accepted. However, the SPC of Sileo did not specify the conditions when the dog should not be left alone and what measures should be taken if the dog becomes sedated.

There were also some points that required further clarification before conclusions can be drawn regarding the reported AEs in the submitted field study. These include providing possible explanations for reported AEs and clarifying the criteria used to assess abnormal values for laboratory variables as clinically relevant or not and summarising abnormal laboratory safety variables to aid assessment. Following the applicant's answers to these questions, the corresponding SPC section might need to be amended to include adverse reactions currently not covered. The frequency of adverse reactions should also be updated as appropriate based on the new data.

Regarding alertness, the somewhat reduced level of alertness compared to the control group was considered expected for the product. "Sedation" is also already mentioned as a common adverse reaction in section 4.6.

It was noted that two dogs received a higher dose than intended which resulted in somnolence or pronounced reduction in alertness. The applicant was asked to provide information on possible explanations for this (e.g., misunderstandings concerning the device/how to administer correct dose) and if there were additional cases of accidental overdosing that did not lead to a reported AE or reduced alertness score.

Additionally, alpha2-agonists are known to cause changes in blood glucose and insulin and can also cause hypothermia. It is noted that hyperglycaemia and decreased body temperature are listed as effects in section 4.10 (overdose). The applicant was asked to comment if additional warnings should be included in

section 4.5, for example, a warning with regards to hypothermia to ensure that treated dogs are not left (alone) in an environment with low ambient temperature.

Following the adoption of the list of questions by the CVMP, the applicant withdrew the present type II variation application.

3. Benefit-risk assessment of the proposed change

Sileo is an oromucosal gel authorised for the alleviation of acute anxiety and fear associated with noise in dogs.

The active substance is dexmedetomidine, an alpha-2 agonist that inhibits the release of noradrenaline from noradrenergic neurons, blocks the startle reflex and thus counteracts arousal.

The proposed variation was to modify the approved indication to include "Alleviation of anxiety and fear associated with owner departure".

3.1. Benefit assessment

Direct therapeutic benefit

As this was a variation to modify the approved indication of the product Sileo, the direct therapeutic benefits would have arisen from the inclusion of this new indication "to alleviate acute anxiety and fear associated with owner separation".

The proposed modification of the indication of Sileo was investigated in one pivotal field study conducted in accordance with GCP. However, following assessment, the CVMP raised concerns regarding the adequacy of the data provided in support of efficacy for the newly proposed indication which precluded firm conclusions. These concerns included the clinical relevance of the outcome from the primary endpoint, the representativeness of included dogs for the entire target population, the selected time frame for efficacy evaluation, and the appropriateness of the short treatment period to successfully manage a chronic condition.

Following the CVMP comments/list of questions, the applicant withdrew this variation application.

3.2. Risk assessment

As this was a variation to introduce an additional indication to existing presentations of the product Sileo, the risk assessment would have focused on potential risks arising from the introduction of the newly proposed indication. However, following the CVMP comments/list of questions, the applicant withdrew this variation application.

Safety:

Risks for the target animal:

The safety of dexmedetomidine hydrochloride in dogs for use for the added indication was evaluated in one pivotal field study conducted in accordance with GCP. The dose (125 µg/m^2) and re-treatment interval (2 h) is proposed to be the same as already authorised for alleviation of fear and anxiety associated with noise, however, the maximum number of doses per day is limited to two for the newly proposed

indication. A maximum treatment duration of 9 days is proposed. Concerns have been raised regarding the safety of the prolonged use since no specific target animal safety study has been conducted in support for the prolonged treatment duration and the clinical field study only evaluated a 2-week treatment phase. A number of other concerns related to safety in the target species have also been raised. No final conclusion could be drawn on safety in the target species until those issues have been satisfactorily addressed.

3.3. Risk management or mitigation measures

Risk management or mitigation measures and appropriate information to be included in the SPC to inform on the potential risks of this product relevant to the target animal were considered pending additional information from the applicant.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, user safety, environmental safety.

In the presence of (major/other) concerns, no conclusions can currently be taken on the benefit-risk balance of the product for the proposed indication "to alleviate acute anxiety and fear associated with owner separation".

4. Conclusion

Based on the original data presented on safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Sileo is not approvable at the present time since "major objections" have currently been identified which preclude a recommendation for variation of the terms to the marketing authorisation.