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Committee for Medicinal Products for Veterinary Use

CVMP assessment report for type II variation for ProZinc (EMEA/V/C/002634/II/0015)

International non-proprietary name: insulin human

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

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Introduction

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Boehringer Ingelheim Vetmedica GmbH (the applicant), submitted to the European Medicines Agency on 29 May 2018 an application for a type II variation for ProZinc.

1.2. Scope of the variation

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

to add a new non-food producing target species (dogs).

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

ProZinc (protamine zinc recombinant human insulin) is a suspension for injection which was initially authorised in July 2013 for subcutaneous administration to cats for the treatment of diabetes mellitus to achieve reduction of hyperglycaemia and improvement of associated clinical signs.

The purpose of this variation application is to include dogs as an additional target species using the same route of administration and indication as already approved for the target species cats.

2.1. Safety

Cross-reference has been made to data previously submitted and assessed by the CVMP, including pharmacology and toxicological data. Only new information/data provided to support the inclusion of dogs as a target species was reviewed in this type II variation application.

2.1.1. User safety

A user safety assessment was provided. It is expected that the risk of accidental exposure will most likely arise from dermal contact or accidental self-injection (both likely to arise from an incorrect injection technique). It can be concluded that a potential risk for hypoglycaemia in the user may result following accidental self-injection but that the risk of such an event may be suitably mitigated by way of adequate training/advice in product administration by the prescribing veterinarian along with the proposed user safety warnings/advice in the product information.

The product has already been approved by the CVMP for subcutaneous administration to cats. The only potential new risk will be from exposure to the possibly larger injection volume required for the dog. The SPC therefore includes a recommendation that suitable training/advice should be provided to the animal owner by the prescribing veterinarian before using for the first time and how symptoms of hypoglycaemia may be treated at home by the animal owner.

2.1.2. Environmental safety

An environmental risk assessment has been provided, which can stop at Phase I. It can be accepted that the product will not present an unacceptable risk to the environment when handled, administered, stored and disposed of in accordance with the recommendations included in the proposed product information.

2.2. Efficacy

2.2.1. Pharmacodynamics/pharmacokinetics, dose justification

The active substance of ProZinc 40 IU/ml suspension for injection is human insulin, which is identical to human endogenous insulin and has been safely used in humans for many decades. ProZinc is a protamine zinc recombinant human insulin suspension for injection.

The applicant has provided an overview of the pharmacodynamic effects of insulin based upon published literature. Insulin acts as a potent mediator of carbohydrate and fat metabolism. In tissues which are insulin-responsive, it facilitates cellular uptake and metabolism of glucose. It exerts its effect by binding to insulin receptors on the plasma membrane of cells. The major primary pharmacodynamic mode of action of insulin is its hypoglycaemic (glucose lowering) effect. No significant differences on the hypoglycaemic effect have been reported in humans between recombinant human insulins or insulins of animal origin (porcine or bovine).

In addition to the data package provided in support of the pharmacodynamics/pharmacokinetics of ProZinc within the context of the original application for marketing authorisation in the target species cats, two new studies have been provided with this variation application to support pharmacodynamics/pharmacokinetics in the newly proposed target species, dogs.

2.2.1.1. Pivotal PK/PD study (study 2010062)

In a prospective laboratory non GLP study, ProZinc was administered subcutaneously to 10 healthy Beagles using an incomplete crossover design at a dose of either 0.3 IU/kg (n=5), 0.5 IU/kg (n=5) or 0.8 IU/kg (all at a single injection site on the lateral thorax) (n=10) or 0.8 IU/kg divided over three separate injection sites (n=6).

Blood glucose and insulin concentrations were assayed in order to estimate the pharmacokinetic profile of insulin and the pharmacodynamic effect of insulin on glucose. Onset of insulin action (time after insulin administration that glucose concentration first became significantly lower than basal levels), time to glucose nadir (time after insulin administration that the lowest glucose concentration was reached), duration of insulin action (time from insulin administration to the time glucose concentrations returned to a value not significantly lower than basal), average insulin and glucose concentrations (determined from the area under the corresponding concentration curve (AUC) between 0 and 24 hours), time to maximum insulin concentration and insulin persistence (calculated as time from insulin administration to the first time point (after an insulin peak) at which insulin concentrations no longer differed from basal levels) were investigated.

Mean or median and range of maximum insulin concentrations, time to maximum insulin concentrations and median and range of the insulin persistence were similar among protocols; median onset of insulin action, time to glucose nadir and duration of insulin action were also found to be similar among protocols, but the ranges were very large.

An acceptable level of tolerance (both systemic and local) was observed in this study.

Findings from this study suggest that, following subcutaneous administration of 0.5 IU/kg (single site injection), onset of insulin action is to be expected around 3 hours (median), maximum insulin concentrations occur at approximately 6 hours (median), 90% of insulin is absorbed within 24 hours, time to glucose nadir is approximately 16 hours (median) and duration of insulin effect lasts for approximately 20 hours (median).

Following subcutaneous administration of 0.8 IU/kg (single site injection), onset of insulin action is to be expected around 4 hours (median), maximum insulin concentrations occur at approximately 8 hours (median), 90% of insulin is absorbed within 24 hours, time to glucose nadir is approximately 14 hours (median) and duration of insulin effect lasts for approximately >24 hours (median). However, significant inter- and intra-animal variability in insulin and glucose concentrations is to be expected.

Following the response to a question raised on the raw data used to establish the PK and PD parameters, the information proposed for inclusion in the SPC has been revised to highlight the high variability observed in time to glucose nadir in dogs (range 3 to >24 hours) and in the duration of insulin action in healthy dogs (range 12 to >24 hours).

2.2.1.2. Pilot exploratory clinical study

The second study was a pilot exploratory clinical study conducted in 17 dogs (6 treatment naïve and 11 previously treated) with persistent fasting hyperglycaemia (blood glucose concentration >250 mg/dl) and persistent glycosuria with or without presentation of clinical signs. In this study, animals commenced insulin therapy using a dose of 0.25 IU/kg twice daily. The study was conducted over a course of a 60-day period.

Findings from this study indicate that, after 60 days of therapy, there was a statistically significant increase in the median dosage of insulin needed, a decrease in mean blood glucose 10-hour curve and a decrease in serum fructosamine concentration.

However, no difference in lowest blood glucose level was observed when comparing Day 60 to Day 1 values. No difference between treatment naïve and previously treated dogs was observed for median insulin dose, mean or lowest blood glucose level or serum fructosamine. Lowest blood glucose values from the 10-hour curve occurred at the beginning (12 hours after insulin administration the previous evening) or at the end of the 10-hour blood sampling interval. This was observed in 54% of the 68 blood glucose

curves, suggesting that the time to maximum hypoglycaemic effect of the product is likely greater than 10 hours.

In addition, it became evident during the course of the study that the initial starting dose of 0.25 IU/kg administered every 12 hours (BID) was insufficient and, by the end of enrolment, a higher starting dose of 0.5 IU/kg (BID) was used.

Acknowledging the limitations of the small study sample size, it would appear that a starting dose of 0.25 IU/kg BID is likely to be inadequate, and that inability to record blood glucose nadirs from the 10-hour blood glucose curves suggests that once daily administration with ProZinc may be adequate in some animals. The adequacy of once or twice daily administration was investigated in field studies.

Based upon the results of these studies, it can be accepted that, in dogs, a starting dose of 0.5-1.0 IU/kg SID appears reasonable for investigation in clinical field trials.

2.2.2. Field studies

2.2.2.1. EU pivotal field study

The results of a well-conducted GCP-compliant pivotal multi-centre clinical field trial conducted in the EU (Germany, Netherlands, France, Spain, UK) and Switzerland were provided, which investigated the effectiveness and tolerance of ProZinc for the control of diabetes in both treatment naïve and previously treated dogs for a period of 84 days. Dogs that completed this study were allowed to continue in an extended use (safety) study, if their diabetes mellitus was considered regulated by the investigators.

A sufficient number of animals were enrolled in the study. Dogs included in the study showed fasting blood glucose concentrations (prior to morning insulin injection in previously treated diabetic dogs) above 250 mg/dl, glucosuria, and at least one clinical sign consistent with diabetes mellitus (polydipsia, polyuria and/or bodyweight loss). ProZinc was compared to an authorised veterinary medicinal product containing insulin, using a non-inferiority design with a non-inferiority margin of Δ=-15%. Justification for the choice of non-inferiority margin was provided and was considered acceptable.

The age, breed, gender and treatment history (pre-treated and naïve) of animals included in the study are sufficiently representative of the intended target population.

The duration of the study was adequate for the purpose of comparing effectiveness of controlling diabetes under field conditions and, in the absence of a specific target animal tolerance study, for assessing tolerance following repeated administration of ProZinc.

The initial starting dose (0.5-1.0 IU insulin/kg SID) is in accordance with the recommendations included in the proposed SPC. A decision tree was used to determine subsequent amendment to the frequency of dose administration (SID or BID) and was based upon the improvement of clinical signs and a cut-off value for maximum blood glucose of 300 mg/dl. However, this decision tree did not appear to be fully adapted to the mode of action of the product that was shown in the study. Indeed, considering the blood glucose curve determination in the study and in comparison with the authorised veterinary medicinal product containing insulin, the reduction of glycaemia in diabetic dogs treated subcutaneously with the product was shown to be gradual and not immediate. In a significant proportion of dogs (67.9%), the maximal action on blood glucose concentrations (i.e. blood glucose nadir) was not observed by the end of the 9 hour period used to determine blood glucose curves in the study and this may explain the increased frequency of hypoglycaemia events that was observed in comparison to the comparator product when using the decision tree for dose adjustment in this study.

Initially proposed recommendations on insulin dose adjustment and choice of dosing scheme were revised

following CVMP questions and are now based upon a combination of measurement of blood glucose and assessment of clinical signs and this choice of criteria is considered appropriate.

The primary efficacy parameter was a composite variable defined as a significant improvement in "Control of Diabetes" compared to Day -1 and was recorded as either treatment 'success' or 'failure'. Treatment success was defined as at least one blood parameter (mean blood glucose, minimum blood glucose, fructosamine) classified as success and at least one clinical parameter (polyuria, polydipsia, or bodyweight) classified as success on the last day of the study.

Results of the analysis indicate that ProZinc was non-inferior to the positive control, with 84.3% of ProZinc-treated dogs and 82.0% of control-treated dogs considered a 'success'. The lower limit of the two-sided 95%-confidence interval (-7.09%) for the difference in success rates lies completely above the non-inferiority margin of Δ=-15%, indicating that ProZinc was non-inferior to the positive control product for success (significant improvement in "Control of Diabetes" compared to Day -1) in the PP population. Non-inferiority was also demonstrated for the ITT population.

Those efficacy percentages were obtained with daily mean doses of insulin of 1.3 IU/kg for SID treatment and 1.6 IU/kg for BID treatment in the ProZinc group, compared to 1.1 IU/kg for SID treatment and 1.4 IU/kg for BID treatment in the control group, from Day 63 until the end the study. Whilst it is noted that the dose of ProZinc was numerically higher than the control products, it was accepted that this difference relates to the different nature of the two insulins and their pharmacological effect.

Secondary efficacy parameters included comparison of both groups in terms of treatment success on the last day (SID or BID), symptomatic hypoglycaemic events during study period, improvement of ketonuria on the last day compared to screening, animal owner's assessment of overall quality of life (QoL) changes and investigator's assessment of dog's overall condition. Results for these secondary efficacy parameters suggest that there was no difference between arms in dogs considered a success on SID insulin administration (83.1%). A higher proportion of dogs on BID insulin were considered a success for ProZinc (86.3%) compared to the positive control (80.8%). More dogs in the ProZinc group were still on SID treatment towards the end of the study compared to the control group (ProZinc group 62.8% and 53%, respectively), but a higher number of animals completed the extended phase of the EU field study on BID treatment in the ProZinc group.

It is noted from two other studies provided with this application that higher percentages of success were reported in treatment naïve dogs compared to previously treated dogs: in one study, 80.3% of treatment-naïve dogs were considered a success versus 61.4% of previously treated dogs; in another study, 90.9% of treatment-naïve dogs were considered a success versus 64.3% of previously treated dogs. Given that less than half of the study population had their diabetes previously treated with insulin, the applicant was asked to provide information to summarise the effect of changing to ProZinc in these (insulin pre-treated) animals in order to determine if a beneficial effect (or otherwise) in diabetic control results from the change in insulin supply from the previously used insulin to ProZinc, and therefore if such a change has been supported by the findings from this study.

Descriptive statistics relating to the proportion of successes in the pivotal EU field study comparing treatment-naïve to previously-treated animals were subsequently provided and indicated that 80.4% of previously-treated dogs were considered a success in the ProZinc treated group compared to 73.2% in the control group. This compared favourably with the 87.2% of treatment-naive dogs considered a success in the ProZinc treated group compared to 90.9% in the control group. It can be accepted that efficacy of ProZinc in previously treated (poorly controlled) diabetic dogs has been suitably demonstrated and that ProZinc can therefore be recommended for the treatment of both treatment-naïve and previously-treated dogs.

In terms of target animal tolerance, slightly more adverse events were reported for the ProZinc group (80.1% of treated dogs) than for the control group (72.3% of treated dogs).

In total, 26.5% of dogs treated with ProZinc and 18.2% of dogs treated with the positive control experienced symptomatic or asymptomatic hypoglycaemic (HG) events. The majority of dogs were observed with non-severe HG events. The proportion of dogs with symptomatic HG events was higher in the ProZinc group (21.7%) than in the control group (10.1%).

Given that the same dosing regimen and guidance relating to dose frequency and adjustment was used for both ProZinc and the control group, the reason for observing a higher proportion of hypoglycaemic events in the ProZinc group was unclear and the applicant was requested to comment on this finding.

In particular, the applicant was asked to identify at what stage (induction or maintenance) of therapy such events were observed and discuss what (if any) measures may need to be taken in order to minimise the occurrence of symptomatic hypoglycaemic events in dogs, and indeed if any increase in events in insulin pre-treated animals changing from another insulin product to ProZinc was evident.

In the response to the above concerns, the applicant highlighted the fact that the study guidance on dose adjustment relied on use of a 9-hour blood glucose curve and that a blood glucose nadir may not have been reached within 9 hours for dogs administered ProZinc and consequently, the dose of ProZinc may have been inappropriately adjusted (increased), resulting in a higher incidence of hypoglycaemic events in the ProZinc-treated dogs. This was supported by a Clinical Expert statement. In addition, following a review of the individual data from dogs that were reported to have symptomatic hypoglycaemia, a distinct blood glucose nadir was not observed prior to the onset of the hypoglycaemic event in 73.3% and 79.2% of ProZinc-treated dogs on SID or BID therapy, respectively, compared with 40% and 44.4% in the control group.

The time between last insulin administration and onset of the symptomatic HG events was also investigated for both treatment groups and this revealed a later onset of HG events in the ProZinc group compared to the positive control group. This difference was evident for the subsets of dogs treated once daily (13.3 hours for ProZinc vs 6.1 hours for positive control), as well as those treated twice daily (9.1 hours for ProZinc vs 5.9 hours for positive control). In this study, 15.3% of dogs in the ProZinc group and 5.1% of dogs in the positive control group (PP population) showed evidence of symptomatic hypoglycaemia while on SID treatment. On BID treatment, 9% of dogs in the ProZinc group and 5.9% of dogs in the positive control group showed evidence of symptomatic hypoglycaemia. These analyses were repeated for the safety population with the same outcome.

In order to mitigate against any risk arising from reliance on blood glucose nadir for the purpose of dose adjustment, the proposed SPC was revised to recommend monitoring for diabetic control (as opposed to blood glucose monitoring) and that blood glucose curves should be conducted over a sufficient period to determine a blood glucose nadir.

In conclusion, considering the results of this pivotal field study, it can be accepted that ProZinc was demonstrated to be non-inferior to the positive control for the control of diabetes mellitus in dogs.

2.2.2.2. USA field study

In further support of the safety and efficacy of ProZinc in dogs, the applicant provided the results of a clinical field study conducted outside the EU (USA). This was an 'open-label' GCP-compliant multi-site field study conducted in 276 diabetic dogs from 17 different study sites. Dogs included in the study showed fasting blood glucose concentrations (prior to insulin injection in previously treated diabetic dogs) above 250 mg/dl, glucosuria, and at least one clinical sign consistent with diabetes mellitus (polydipsia, polyuria

and/or bodyweight loss). 44.3% of the animals in the 'Efficacy' population were previously treated animals, whereas 55.7% were treatment naïve.

The study was divided into two phases – phase I lasted 84 days and phase II (extended phase) lasted 98 days. All study animals were administered ProZinc as no control group was included in the design. The absence of a positive control group is considered to be a deficiency in this study's design and, as a result, it is considered more difficult to definitively attribute any improvement in diabetes control solely to the investigational product.

As in the pivotal EU field trial, the primary efficacy parameter consisted of a composite variable evaluated at Day 84 and compared to baseline with the result recorded as either success or failure. Treatment success was defined as improvement in at least one clinical parameter (polyuria, polydipsia, or body weight) and improvement by one category in at least one laboratory parameter (mean blood glucose, minimum blood glucose, or fructosamine). Secondary efficacy parameters differed from the parameters applied in the EU study, and included animal owner's assessment of animal quality of life (QoL) and behaviour, treatment success on Day 84, comparison of BID and SID treatment effects, insulin dose and frequency, physical and laboratory examinations, and the incidence of hypoglycaemic blood values.

Starting dose was 0.5 - 1.0 IU/kg SID every morning, with a decision to switch to BID dosing made by Day 42 at the latest. Efficacy was considered demonstrated if the lower bound of the 95% confidence interval for the estimate of the percentage of 'successes' was >60%. Although the applicant has clarified that this criteria for percentage success was agreed by the regulatory authority in the USA where the study was conducted, no further detail was provided on what basis this value has been selected. Results from this study indicate that the criteria for demonstrating efficacy (at day 84) have been met; that is, the lower bound of the 95% CI for the estimate of percentage of 'successes' was greater than 60% using the 'Efficacy' population dataset.

Results for polyuria, polydipsia and bodyweight at Day 84 suggest that 83.8%, 83.3% and 49.1% of animals in the 'Efficacy' population were considered a success for each parameter, respectively. In addition, results for mean blood glucose, minimum blood glucose and fructosamine at Day 84 suggest that 58.8%, 54.8% and 52.2% of animals in the 'Efficacy' population were considered a success for each parameter, respectively.

The percentage efficacy (72.1%) is below 75% and is less than in the EU pivotal field study (84.3%). The applicant claimed that "it is possible the failure cases were under-dosed." The applicant listed the failure cases and the actual doses of ProZinc received by those cases, but the design of the study does not allow any firm conclusion on this hypothesis.

At Day 84, the percentage of successes in treatment naïve dogs was numerically higher for both SID and BID dosing (79% and 82%, respectively) compared to previously treated dogs (58% and 66%, respectively). The reason for this apparent difference in response to ProZinc therapy between treatment naïve and previously treated animals is unclear.

It can be accepted that the findings from this study suggest an acceptable overall tolerance profile following ProZinc administration to both treatment naïve and previously treated diabetic dogs.

However, as injection site reactions were reported in 5 dogs (1 pain, 2 lumps and 2 lesions) out of the 276 dogs included in the safety population, the possibility for injection site reactions was included in section 4.6 of the SPC.

Given the deficiencies noted, the findings of this study cannot be considered pivotal and may only be considered supportive of the pivotal EU field efficacy study.

2.2.2.3. Japan field study

The results of a further field study conducted in Japan were provided. This study was a GCP-compliant study conducted at 13 study sites and followed the same design as the study conducted in the USA, but only included a single 84-day phase. A total of 30 diabetic dogs were enrolled with 14 being treatment naïve and 16 previously treated with insulin. All study animals were administered insulin as no control group was included in the design. The absence of a positive control group is considered to be a deficiency in this study's design and, as a result, it is considered more difficult to definitively attribute any improvement in diabetes control solely to the investigational product. In addition, no study protocol or certificate of analysis for the investigational product has been provided. However, the applicant confirmed that the investigational product used was ProZinc.

The primary efficacy variable consisted of a composite variable evaluated at Day 84 and compared to baseline with the result recorded as either success or failure. Treatment success was defined as improvement in at least one clinical parameter (polyuria, polydipsia, or body weight) and improvement by one category in at least one laboratory parameter (mean blood glucose, minimum blood glucose, or fructosamine). Starting dose was 0.5 - 1.0 IU/kg SID every morning, with a decision on whether to switch to BID dosing or not made by Day 42 at the latest.

In this study, efficacy was considered demonstrated if the percentage of dogs considered a treatment success was high enough to be considered as 'clinically meaningful'. The CVMP is of the opinion that the use of a non-specific threshold such as this is meaningless and unsuitable for the purpose of determining efficacy. Notwithstanding the above, the results from this study indicate that 19/25 (76%) dogs were considered to be a treatment success based upon the 'Efficacy' population dataset, indicating that over three quarters of the study animals responded to product administration in terms of both an improvement of at least one category in at least one laboratory parameter (mean blood glucose, minimum blood glucose, or fructosamine) and improvement in at least one clinical parameter (polyuria, polydipsia, or body weight).

Further, results for polyuria, polydipsia and bodyweight at Day 84 suggest that 86.4%, 81.8% and 86.4% of animals in the 'Efficacy' population had improved for each parameter, respectively. In addition, results for mean blood glucose, minimum blood glucose and fructosamine at Day 84 suggest that 81.8%, 68.2% and 90.9% of animals in the 'Efficacy' population had improved for each parameter, respectively.

Mean insulin dose at Day 7 was 0.6 IU/kg/day (SID). By Day 84, the mean SID dose was 0.9 IU/kg/day and the mean BID dose (per dose) was 0.9 IU/kg/day. The mean dose considered necessary to control diabetes in the study animals in this study at Day 84 (0.9 IU/kg/day SID) is considerably lower than that considered necessary at the same time point (Day 84) in the USA field study (1.43 IU/kg/day SID) and in the EU field trial (1.3 IU/kg/day SID). The reason for this is somewhat unclear.

As observed in the USA study, it is noted that at Day 84, the percentage of successes in treatment naïve dogs was numerically higher (100%) compared to previously treated dogs (75%). The reason for this apparent difference in response to insulin therapy between treatment naïve and previously treated animals is unclear.

Given the deficiencies noted, and the small sample size of 30 dogs, the findings of this study cannot be considered pivotal and may only be considered supportive of the pivotal EU field efficacy study.

2.2.3. Target animal tolerance

No specific target animal tolerance study in dogs has been conducted; instead, safety of the product was supported by the tolerance data reported for the pivotal EU field study and the field studies conducted in

Japan and the USA. In addition, the applicant provided the results of an "extended use (safety) field study" (study 2012034).

The applicant justified this approach on the basis that according to Annex I of Directive 2009/9/EC and the Guideline on target animal safety for veterinary pharmaceutical products (VICH Topic GL43), target animal safety data could be derived from both studies under laboratory conditions or field studies conducted according to VICH GCP. Also, for animal welfare reasons, a classically-designed overdose target animal safety study was considered to be inappropriate, since it is well-known that an overdose of insulin in healthy dogs will result in severe hypoglycaemia, most likely leading to death.

The CVMP accepted this justification and the approach used by the applicant to support target animal tolerance by assessing safety within the context of field studies (including extended field use studies, thereby satisfying the requirement of GL43 for an adequate assessment of tolerance to prolonged administration of the product) where the product is administered as intended in practice is considered acceptable. Tolerance has therefore been assessed within the context of the field studies.

2.2.3.1. Extended use (safety) field study

This GCP-compliant study was a follow-up from the pivotal EU field study and conducted at the same sites within the EU as in the pivotal EU study. Dogs which had successfully completed the pivotal EU field study were eligible for inclusion in this extended use study for an additional 98 days of treatment, designed to focus on tolerance.

In this study, the enrolled dogs were administered ProZinc and a slightly lower number of dogs were administered a positive control, i.e. an authorised veterinary medicinal product containing insulin.

The number of study animals and the parameters measured (clinical signs, haematology, biochemistry, urinalysis, owners' assessment, investigators' assessment) can be accepted as suitably comprehensive for the intended purpose of this study to assess target animal tolerance. Given the absence of treatment-naïve dogs in this study, tolerance to the introduction of initial treatment with ProZinc has obviously not been investigated in this study here.

The frequency of adverse events was similar between dogs administered ProZinc and those administered the positive control (71.7% and 72%, respectively) with the most frequently reported adverse event being hypoglycaemia occurring in 19.7% of ProZinc-treated dogs and 17.8% of control dogs, which was lower than in the pivotal EU field study. Six dogs in the ProZinc-treated group died or were euthanised; this was not considered to have been treatment-related by the study investigators; however, the applicant was asked to provide further information/detail on the two animals that were found dead. Based upon the information provided, it can be accepted that neither death may be considered attributable to product administration.

The results of this 'extended use' study provide evidence of an acceptable tolerance profile of ProZinc when administered in accordance with proposed dosing recommendations in animals with existing diabetes for which good control has already been attained.

It is noted that the frequency of both dosage regimens is somewhat altered in comparison to that recorded during the pivotal EU study (62.8% of dogs on ProZinc vs 53% of control dogs at SID at day 63). For both treatments, the proportion of dogs on SID regimen subsequently decreased (Day 63 phase I and D0 and D70 of Phase II), with dose adjustments based on the same guidance as that of the pivotal field study. However, the initially proposed recommendations on insulin dose adjustment and choice of dosing scheme were revised following CVMP questions and are now based upon a combination of measurement of blood glucose and assessment of clinical signs.

In addition to the safety evaluation, an investigator assessment was planned at visit Day 28, 70, 98 for the dog's condition and overall control of diabetes. At day 0, 91/111 (82.0%) of dogs in the ProZinc group and 89/98 (90.8%) of dogs in the positive control group were rated as good or excellent by the investigators. In the ProZinc group the proportion of dogs rated as good or excellent slightly increased until day 98 to 84.7%, whereas in the positive control group the proportion of dogs rated as good or excellent decreased during the study to 82.6% of dogs.

2.2.3.2. Overall conclusions on tolerance

In the absence of a specific target animal tolerance study, tolerance was assessed in the three field studies (including an extended use safety study).

In the pivotal EU field trial, 76.4% of the Safety population experienced an adverse event, with slightly more adverse events being reported for the ProZinc group (80.1% of treated dogs) than for the control group (72.3% of treated dogs). Most frequently reported adverse events following administration of ProZinc were hypoglycaemia (26.5% of dogs), cataract, urine abnormalities, otitis externa, emesis, anorexia, lethargy, diarrhoea and conjunctivitis.

Based on the per protocol population dataset, 21.7% of animals in the ProZinc group had at least one symptomatic hypoglycaemic event compared with 10.1% in the control group. Further, ten dogs in the ProZinc group had more than two symptomatic hypoglycaemic events compared with none in the control group. Given that the same dosing regimen and guidance relating to dose frequency and adjustment was used in both the ProZinc and control groups, the applicant was requested to comment on what appears to have been a higher (two-fold) incidence of symptomatic hypoglycaemic events in the ProZinc-treated group compared to the control group.

The applicant clarified that as a blood glucose nadir may not have been reached within 9 hours for dogs administered ProZinc, the dose of ProZinc may have been inappropriately adjusted (increased), resulting in a higher incidence of hypoglycaemic events in the ProZinc-treated dogs. In addition, following a review of the individual data from dogs that were reported to have symptomatic hypoglycaemia, a distinct blood glucose nadir was not observed prior to the onset of the hypoglycaemic event in 73.3% and 79.2% of ProZinc-treated dogs on SID or BID therapy, respectively, compared with 40% and 44.4% in the control group.

In order to mitigate against any risk arising from reliance on blood glucose nadir for the purpose of dose adjustment, the proposed SPC was revised to recommend monitoring for diabetic control (as opposed to blood glucose monitoring) and that blood glucose curves should be conducted over a sufficient period to determine a blood glucose nadir.

In all the studies, hypoglycaemic reactions were very commonly reported (up to 26.5% of treated dogs), and varied from "asymptomatic" to the typical signs consistent with hypoglycaemia (e.g. lethargy, ataxia, seizure).

In the USA field study, the most commonly reported adverse events were vomiting, inappetence/anorexia, lethargy, seizure/collapse/ataxia, diarrhoea/blood in faeces/enteritis, hypoglycaemia, cataract. Hypoglycaemia was the most frequently reported adverse event considered possibly related to the administration of ProZinc, with a total of 79 hypoglycaemic events recorded (46.8% of which were associated with clinical signs). Local adverse events were reported in 5 dogs.

In the study conducted in Japan, only a small sample size was included and, consequently, only nine adverse events were reported: hypoglycaemia, emesis, bacterial dermatitis, otitis externa and cystitis.

In the extended use safety study, the frequency of adverse events was similar between dogs

administered ProZinc and those administered the control product (71.7% and 72%, respectively), with the most frequently reported adverse event being hypoglycaemia occurring in 19.7% of ProZinc-treated dogs and 17.8% of dogs in the control group. Two animals were found dead but their deaths were not considered to be treatment-related.

Overall, it is considered that the adverse reaction observed in field studies and considered to be treatment-related (hypoglycaemia) is properly reflected in the product information, along with measures to mitigate against the risk.

Amendment of the PSUR cycle is considered appropriate to ensure adequate pharmacovigilance monitoring due to the addition of a new target species (dogs) and given that the applicant has agreed to implement the CVMP revised recommendation for basic surveillance of EVVet data and to submit all adverse events electronically. PSURs covering all authorised presentations of the product will be submitted as follows: the next PSUR will cover 1 August 2017 - 31 January 2020, followed by a PSUR covering 1 February 2020 - 31 July 2020 and thereafter PSURs should be submitted at 3 yearly intervals, unless otherwise required.

3. Benefit-risk assessment of the proposed change

ProZinc is currently authorised for the treatment of diabetes mellitus in cats to achieve reduction of hyperglycaemia and improvement of associated clinical signs. The active substance is insulin human (produced by recombinant DNA technology). Insulin activates insulin receptors and therewith a complex cell signalling cascade which results in increased glucose uptake into the cells. The main effects of insulin are the reduction in circulating blood glucose concentrations and the storage of fat. The initial recommended dose in cats is 0.2 to 0.4 IU/kg bodyweight every 12 hours. For cats previously controlled on insulin, a higher starting dose up to 0.7 IU/kg bodyweight may be appropriate. The product is a suspension for subcutaneous injection.

The proposed variation is to add a new non-food producing target species (dogs).

3.1. Benefit assessment

Direct therapeutic benefit

The direct benefits arise from the possibility to treat dogs with the product. The proposed indication is for the treatment of diabetes mellitus in dogs to achieve reduction of hyperglycaemia and improvement of associated clinical signs.

The effectiveness of the product for the above indication was investigated in a number of field studies, both within and outside the EU. The pivotal field study was conducted within the EU in a significant number of dogs and results from that study suggest that the product is as effective (non-inferior) as another insulin-containing product authorised in the EU for the treatment of diabetes mellitus in dogs.

Treatment effect was defined as a significant improvement in "Control of Diabetes" compared to Day -1 and was recorded as either treatment ‘success’ or ‘failure’. Treatment success was defined as at least one blood parameter (mean blood glucose, minimum blood glucose, fructosamine) classified as success and at least one clinical parameter (polyuria, polydipsia, or bodyweight) classified as success on Day 84. Results indicate that ProZinc was non-inferior to the control product with 84.3% of ProZinc-treated dogs and 82.0% of dogs in the control group considered a ‘success’.

It can be accepted that efficacy of ProZinc in previously treated (poorly controlled) diabetic dogs has been suitably demonstrated and that ProZinc can therefore be recommended for the treatment of both treatment-naïve and previously-treated dogs.

Additional benefits

The product increases the range of available treatment possibilities for dogs against diabetes.

3.2. Risk assessment

Quality:

Not applicable.

Safety:

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

Administration of ProZinc in accordance with SPC recommendations is generally well tolerated. The main reported adverse reactions include hypoglycaemia and this is indicated in the proposed product information along with measures to mitigate against this risk.

Information on the potential for injection site reactions has been included in the SPC.

Risk for the user:

Although it is acknowledged that there is the potential for a greater risk to the user from use of the product in dogs compared with cats (due to the larger injection volume required for the former), the CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. In order to minimise the risk of accidental self-injection, a recommendation that the prescribing veterinarian ensures that the animal owner receives adequate instruction/training on correct injection technique to ensure both, their own and the animal's safety has been included in the SPC.

Risk for the environment:

ProZinc is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the product information.

3.3. Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal and user and to provide advice on how to prevent or reduce these risks.

Amendment of the PSUR cycle is considered appropriate to ensure adequate pharmacovigilance monitoring due to the addition of a new target species (dogs) and given that the applicant has agreed to implement the CVMP revised recommendation for basic surveillance of EVVet data and to submit all adverse events electronically.

User safety:

It is expected that the risk of accidental exposure will most likely arise from dermal contact or accidental self-injection (both likely to arise from an incorrect injection technique). It can be concluded that a potential risk for hypoglycaemia in the user may result following accidental self-injection but that the risk of such an event may be suitably mitigated by way of adequate training/advice in product administration by the prescribing veterinarian along with the proposed user safety warnings/advice in the product information.

The SPC includes risk mitigation advice indicating that suitable training/advice should be provided to the animal owner by the prescribing veterinarian before using for the first time and how symptoms of hypoglycaemia may be treated at home by the animal owner.

Environmental safety:

An environmental risk assessment has been provided and it can be accepted that as the product will not present an unacceptable risk to the environment when handled, administered, stored and disposed of in accordance with the recommendations included in the proposed product information.

3.4. Evaluation of the benefit-risk balance

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

Based on the data presented, the overall benefit-risk is deemed positive.

The product has been shown to be efficacious for the treatment of diabetes mellitus in the new target species dogs to achieve reduction of hyperglycaemia and improvement of associated clinical signs.

The product is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended.

Appropriate precautionary measures have been included in the SPC and other product information.

4. Conclusion

Based on the original and complementary data presented on safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for ProZinc can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows: to add dogs as a new non-food producing target species for the same indication: treatment of diabetes mellitus to achieve reduction of hyperglycaemia and improvement of associated clinical signs.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I, II, IIIA, IIIB and A.

As a consequence of this variation, sections 1, 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 4.10 and 5.1 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.