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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a variation requiring assessment for Rabitec (EMEA/V/C/004387/VRA/0011)

Vaccine common name: Rabies vaccine (live, oral) for foxes and raccoon dogs

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 62 of Regulation (EU) 2019/6, the marketing authorisation holder, CEVA Santé Animale (the applicant), submitted to the European Medicines Agency (the Agency) on 24 August 2023 an application for a variation requiring assessment for Rabitec.

1.2. Scope of the variation

Variation(s) requested	
I.II.1.c	I.II.1.c - Changes to strength, pharmaceutical form and route of administration - Change or addition of a new strength/potency

The scope of the variation is to add:

- a new a strength (infectivity titre) including a new target species (dogs)
- a new composition of the bait (for the new target species dogs)
- a new vaccine container (sachet - for the new 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 2, Part 3 and Part 4

1.4. Scientific advice

The applicant received scientific advice from the CVMP in September 2020 (EMA/CVMP/SAWP/319098/2020). The scientific advice pertained to safety and efficacy of the dossier.

In the respective scientific advice, it was agreed to apply for the addition of dogs inaccessible to parenteral vaccination as target species for Rabitec. However, oral vaccination in dogs requires a higher potency compared to foxes and raccoon dogs. Therefore, it was recommended to perform a line extension for a new target species, which results in a separate product information for Rabitec when used in dogs not accessible to parenteral vaccination. The applicant followed this advice. The legal basis changed in the meantime; therefore, the application was submitted as variation requiring assessment (VRA) with an extended timetable.

The conditions for acceptance of the addition provided in the responses to the scientific advice were the demonstration of a positive benefit/risk balance for the target species and species category (free roaming dogs) and the submission of an updated risk assessment taking into consideration the different behaviours, preferences and habitats of the different target species. Any new or additional risks identified were to be considered for any studies performed and possible necessary mitigation measures for use in the field should be established. The risk assessment in Part 3 of the dossier was updated concerning the new target species dogs.

Furthermore, the applicant applied for the possibility to omit further safety studies in dogs, as some safety data in dogs were already generated during the marketing authorisation procedure for Rabitec for foxes and raccoon dogs. Even though this data does not completely comply with monograph Ph. Eur. 746 in number of animals and dosage of the vaccine, the results were convincing that the safety of Rabitec is considered

sufficient to waive additional safety studies in dogs, also in regard to the 3Rs principles.
Additionally, safety data from field studies from outside Europe are presented in the current application. Moreover, detailed information on the new bait material is provided and data from field studies is discussed in regard of the impact of the change of the bait material on acceptance in the new target species.

A further point for discussion was the applicants' proposal to set up immunogenicity testing according to the requirements for foxes and raccoon dogs in Ph. Eur. monograph 0746 and to omit field testing also for dogs. The CVMP agreed with the applicants' proposals, provided a MUMS status would be granted for dogs inaccessible to parenteral vaccination. This status was granted by EMA in December 2020. Even though the MUMS principle is no longer established as such in the new legislation, the decision and the resulting requirements for relevant studies are still valid.

Lastly, the applicant proposed to use the serum response 4 weeks post vaccination as measured by a virus neutralisation assay (e.g. RFFIT (rapid fluorescent foci inhibition test), FAVN (fluorescent antibody virus neutralisation)) or the BioPro ELISA test as indicator for immunogenicity in the target species. This excludes the pivotal efficacy study which is performed as challenge study.
The CVMP considered both tests (VN-test or ELISA) as suitable indicators for immunogenicity.

1.5. Limited market status

Not applicable.

2. Scientific Overview

Rabies is a viral zoonotic disease responsible for many human deaths world-wide each year, most of these cases are due to rabies transmitted by free-roaming dogs which are considered to be reservoir of the rabies virus.
Moreover, there is a risk for re-introduction of rabies to the wildlife by dog bites.

In developed countries, dog-transmitted rabies has been largely eliminated by mass vaccination of dogs and further management measures, but globally the dog is the most important reservoir, particularly in developing countries.

Currently, Rabitec is registered for the oral immunisation of foxes and raccoon dogs. With this application the applicant wishes to add dogs not accessible to parenteral vaccination as target species for Rabitec.

To support the proposed claims, new efficacy data of Rabitec in dogs are provided and already available data for safety are discussed.

Due to the slightly different preferences and behaviours of dogs and foxes or raccoon dogs a new composition of the bait, more attractive to dogs, and a new vaccine container (a sachet instead of a blister package) are also introduced. The vaccine is presented in a different strength and dose volume, resulting in a higher maximum titre.

These differences result in a separate product literature for the new target species (dog) which is presented with this application. CVMP comments to the product information are presented in a separate document to this assessment report.

Scientific Advice from December 2020

The applicant followed the scientific advice received from CVMP in 2020.

It was recommended to submit the addition of dogs as a line extension. However, the legal basis changed since the scientific advice in 2020. Therefore, the application was submitted as a variation requiring assessment (VRA) with an extended timetable.

The conditions for acceptance of the addition provided in the responses to the scientific advice were the demonstration of a positive benefit/risk balance for the target species and species category (free roaming dogs). These conditions were fulfilled.

Concerning safety, it was agreed to omit further safety studies.
No serious adverse events were observed in the additional field studies in dogs presented in this variation application. These studies were mainly performed for selection of bait materials attractive to dogs and demonstration of immunogenicity of the vaccine strain SPBN GASGAS in local dogs in the field.

In the scientific advice, the applicant proposed to use the serum response 4 weeks post vaccination as measured by a virus neutralisation assay (e.g. RFFIT, FAVN) or the BioPro ELISA test as indicator for immunogenicity in the target species. The CVMP considered both tests (VN-test or ELISA) as suitable indicators for immunogenicity.

The BioPro ELISA and RFFIT test used for generation of serology data, were used in parallel in several of the field studies provided. Serology data for the pivotal efficacy data was determined by the ELISA test and showed excellent correlation with the results from the challenge.

Quality

The applicant now proposes a maximum titre of $10^{9.0}$ FFU/ml or $10^{9.5}$ FFU/dose of 3 ml for use in dogs instead of the maximum titre of $10^{8.6}$ FFU/dose. A new antigen manufacture method on suspension cells allows the production of batches with higher titres. In the scientific advice from 2020, the CVMP agreed that it is not considered necessary to conduct further safety studies, even though the standard 10-fold overdose study has not been conducted in dogs. This decision was based on the overall safety data available (including a 3-fold overdose study in dogs) and in line with 3Rs principles. In the scientific advice the applicant stated, "For the current Rabitec MA a dose volume of 1.7 ml and a titre range of $10^{6.8}$ – $10^{8.1}$ FFU per dose are specified. For dogs, a higher dose volume (3 ml) and a higher dose range ($10^{8.1}$ – $10^{8.6}$ FFU per dose) is needed."

The higher dose $10^{8.6}$ FFU per dose was used to justify that the overdose studies carried out in dogs in the original MA (with $10^{9.1}$ FFU per dose), represented a 3-fold overdose. CVMP agreed that based on the 3Rs principles and the overall safety data available, the conduct of a new 10-fold overdose study in dogs was not necessary. Therefore, a maximum titre for dogs should be defined, e.g. as $10^{8.6}$ FFU per dose considering the maximum virus titre for which safety has been justified according to the requirements, unless a higher one can be justified.

The applicant provides a justification for the proposed maximum titre of $10^{9.0}$ FFU/ml, as with the newly approved antigen manufacturing process in suspension cells, as recently approved in variation procedure EMEA/V/C/004387/VRA/0012, a maximum titre of $10^{9.0}$ FFU/ml is now achievable.

The intrinsic variability of the titration method is 0.4 $\log_{10}$ FFU/ml, which is typical for this kind of viral titration method and usually accepted to be up to maximally 0.5 $\log_{10}$ FFU/ml. To further support this specification for variability, the applicant provides data from a study report.

The applicant is concerned by the possible consequences of using lower antigen titres in routine production. Namely, the increased risk of non-conform batch testing results and subsequently non-availability of the product for dogs to the market. This should preferably be avoided, considering the WHOs strategy: "Zero by 30: the global strategic plan to end human deaths from dog-mediated rabies by 2030" in which every available vaccine batch against rabies is considered valuable.

As the CVMP agreed in the scientific advice from 2020, no further studies on the safety of overdoses for Rabitec were to be performed. However, some new safety data from field studies for the development of bait materials for dogs are provided. No serious adverse events were observed in any of these studies.

The safety profile of Rabitec in dogs was first discussed during a scientific advice in 2020.
At that time, the decision to accept the omission of further safety studies in dogs, was based on a remaining calculated 3-fold overdose, resulting from the relevant non-target species study submitted with the initial marketing authorisation for foxes and raccoon dogs. Results were assessed as convincing that the safety of Rabitec is considered sufficient to waive additional safety studies in dogs.

The safety profile of the vaccine strain SPBN GASGAS is considered very good and it is not considered likely, that the proposed increase of the maximum release titre will change the safety profile of Rabitec perceptibly, even if it slightly exceeds the maximum titre for which safety was demonstrated in a clinical study in dogs.

Furthermore, during this variation also safety of human exposure to the product via baits in the environment was discussed extensively. In this context, per WOAH requirement the applicant used a statistical model, analysing the likelihood of human exposure to baits in the environment and the following probability of serious adverse events in humans. Results showed that no serious adverse events in humans were to be expected, even in some worst case scenarios e.g. including repeated exposure to baits.

Finally, recently (October 2023), the tripartite, WHO, WOAH and FAO, endorsed and published new guidelines for Oral Vaccination of Dogs against Rabies. This document contains recommendations on how to deal with possible human contacts with the vaccine virus. Due to the safety profile of Rabitec, the requirement for Post-Exposure Prophylaxis (PEP) after direct or indirect exposure to the vaccine virus has been adapted. PEP is no longer required, except when the person is immune compromised.
In this case, PEP is suggested when the vaccine exposure involved intramuscular, intraperitoneal or intracranial inoculation.

Safety of the product Rabitec was assessed as very good in the target species, several laboratory animals and non-target species and in case of (possible repeated) accidental human exposure.

Therefore, the CVMP considers it not feasible to request further justification on the safety profile of Rabitec with a higher maximum release titre from the applicant, even if the newly proposed maximum release titre, slightly exceeds the maximum titre for which safety was demonstrated in a clinical study in dogs.

In summary, from all data provided for the scientific advices and the current variations VRA0011 and VRA0012, in the CVMP's view it is not considered likely, that the proposed slightly higher maximum release titre will result in an increased safety risk for the target animal, non-target animal accidentally exposed humans or the environment.

From the additional information and reasoning provided by the applicant and considering the overall very good safety profile of the vaccine strain SPBN GASGAS as discussed during the scientific advice and variation procedures, a maximum titre of $10^{9.0}$ FFU/ml ($10^{9.5}$ FFU/dose) for Rabitec when used in dogs is considered sufficiently justified.

The materials used for production and the description of their handling are considered satisfactory.
However, further confirmatory information needs to be provided on the details and validation of sterilisation of the foil to be used for sachet production by gamma radiation. The applicant provided a commitment letter, which indicates that data on the sterilisation of the foil used will be provided as soon as they are available but before the end of 2024 at the latest.

All information concerning the manufacturing of the new egg bait matrix material is included in the dossier. The production steps are identical to those for the fishmeal existing bait, only the components and the embedded vaccine container differ. The information provided on manufacture of the egg bait for dogs is

considered satisfactory.

New starting materials added to the dossier are whole egg powder and glycerine for production of the bait matrix. Relevant certificates on the new starting materials are provided and satisfactory. Relevant test and specifications are also provided and satisfactory.

Information on the starting materials used for the production of the new egg bait is considered complete and satisfactory.

Part 2.D. of the dossier concerning control tests during the manufacturing process, was updated concerning the bait mass of the egg bait and the new vaccine container (sachet).

Part 2.E of the dossier concerning final product testing was updated with the specifications for final product testing for the new vaccine container (sachet) and the new egg bait. The updated and newly added information in Part 2.E. is satisfactory.

In-process control and final batch testing results for three consecutive batches of sachets containing the virus suspension are presented.

All data are well within specifications. The respective batch release protocols are provided and satisfactory. However, the certificates mention a different minimum release titre as the certificates were prepared in 2021 and the final value was only established after statistical analysis of stability data.

All data on the bait manufacturing process and the related consistency data on the baiting process are included in the relevant parts of the dossier. The amended dossier pages of Part 2.F.3. including the results from VRA 012, which was ongoing in parallel and is now finalised, are also provided.

Extraneous agents testing was still performed at the time of preparation of the batches; however, it will be omitted for routine testing of commercial batches.

The updated and newly added information in Part 2.F. is satisfactory for the sachet containing the virus suspension.

The applicant provides stability data for sachets, which were stored for up to 27 months at -40°C / -20C°.

The applicant concludes that the product is stable for 24 months when stored at -20°C or -40°C ± 5°C with a minimum release titre of $10^{7.9}$ FFU/ml. However, the titre values on D0 of the stability studies were $10^{8.3}$ FFU/ml for all batches included in the stability study, which is way above the proposed minimum titre of ≥ $10^{7.9}$ FFU/ml. The applicant already indicated that a further stability study is planned including batches, which are closer to the proposed minimum release titre.

Data were analysed by a multiple linear regression model and observed losses have been taken into account in setting the release titer.

During variation procedure EMEA/V/C004387/VRA0012 a storage period of 6 months at -20°C was accepted. Additionally, a storage period of 12 months at -40 °C was accepted. The applicant committed to submit the stability data for the storage of the finished product at -20 °C and at -40 °C for 27 months as soon as the data are available.
The applicant provides stability data for the egg bait material stored between 0 and 47 months.
No significant changes in colour and shape or integrity of the bait material were observed in any of the samples. Additionally, bait acceptance for baits of different ages, including at the end of shelf life, was tested in the field. The acceptance rate achieved in this study corresponds with other studies from literature.

Stability data for the sachets under stress conditions are provided.

All three batches included in the stability study showed stable values for the virus titre and pH value when stored at +25°C for 14 days or +2°C to +8°C for 90 days.

The applicant therefore claims a storage for not more than 28 days at +2-8°C or not more than 5 days at 25°C. These claims are accepted. A cold chain transport is required for the final product consisting of the sachet containing the virus suspension embedded in the bait.

Information on development, manufacture and control of the new vaccine container (sachet) has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety

In one of the safety studies in the original authorisation procedure for Rabitec, safety in dogs as a non-target species was monitored. The study fulfils the requirements for safety in the target animal, except for the number of dogs that were monitored and the titre of the vaccine used (not a 10-fold overdose).

As the titre used for vaccination in dogs is higher than that for foxes and raccoon dogs, the overdose ($10^{9.1}$ FFU) tested in dogs was not a 10-fold overdose. The CVMP agreed to the applicants' request to omit further safety studies in the scientific advice from 2020, as results were convincing that the safety of Rabitec is considered sufficient to waive additional safety studies in dogs, also in regard to the 3Rs principles.

Safety of the product was overall assessed as very good in the target species, several laboratory animals and non-target species and in case of (possible repeated) accidental human exposure.

Therefore, the CVMP considers it not feasible to request further justification on the safety profile of Rabitec from the applicant. The safety profile of the vaccine strain SPBN GASGAS is considered very good and it is not expected that the proposed increase of the maximum release titre will change the safety profile of Rabitec perceptibly.

Should the justification for the higher maximum release titre be considered as not sufficient by CVMP, the applicant would have to carry out an additional safety study in dogs, to establish the higher maximum release titre and to ensure continued availability of the product for dogs. In the CVMP's opinion, this should be avoided in line with the 3R principles as already discussed during the 2020 scientific advice.

In summary, in the CVMP's view it is not to be expected that the proposed slightly higher maximum release titre will result in an increased risk for the target animal, non-target animal accidentally exposed humans or the environment, as the safety profile of the vaccine strain SPBN GASGAS was assessed as very good and it is not expected that the proposed increase of the maximum release titre will change the safety profile of Rabitec perceptibly, even if it exceeds the maximum titre of the batch which was used in a dog safety study.

The CVMP is therefore prepared to accept the proposed maximum release titre of 9.0 $\log_{10}$ FFU/ml (9.5 $\log_{10}$ FFU/dose).

Some additional data is provided from field studies, which were performed in several countries, with the main purpose to select an appropriate bait material attractive to dogs. No severe adverse events occurred during these studies.

During the marketing authorisation procedure for foxes and raccoon dogs, data on pregnant and lactating animals were generated. Fox and raccoon dog belong to the family Canidae and, thus, both are susceptible to rabies. In an overdose safety study in raccoon dogs, it was shown that the vaccine virus does not disseminate to the gonads. A study on the vertical transmission and safety in pregnant animals of the rabies vaccine strain SPBN GASGAS in–foxes–was performed during the original authorisation procedure.

None of the treated vixens or untreated cubs showed any clinical signs of rabies or died after vaccination from causes attributable to the vaccine; no adverse effects on the pregnancy or the offspring were noted.

The claim on the use during pregnancy and lactation in dogs, based on the data gathered in field studies and

also based on safety shown in other canid species can be accepted.

Concerning the formal updates in the safety part of the dossier, satisfactory amendments of Part 3D of the dossier, the environmental risk assessment were made. Section D.4. 'Assessment of level of risk' was revised satisfactorily and information on the distribution method and mitigation measures related to a possible human exposure was added.

Furthermore, section 3B.7 User safety was updated with the information on the new materials and the different distribution method (hand-out and retrieval instead of aerial distribution). The major concern about an accidental exposure of humans and uncertainties of the planned immunisation method by an individual offer of baited sachets was cleared. Detailed information about the separate steps during the hand/out and retrieval procedure (e.g., as a flow-chart) are provided. Further data on the risk assessment for human exposure to the vaccine are provided. The same label which is used for the product for foxes and raccoon dogs will be put on the baits for dogs. It contains a warning statement (Do not touch!), a pictogram and a QR code. The warning statement was also added to the sachet. The respective amended product literature is provided.

The information on the details of hand-out and retrieve model (HORM) and the human safety assessment for Rabitec provided is sufficient to assess the risk of human exposure and the probability of baits remaining in the environment. The risk for human exposure is considered as low and the subsequent risk for the occurrence of serious adverse events in humans is assessed as even lower.

It is considered that the newly-developed combination of a sachet as vaccine container and an egg-flavoured bait with a slightly higher volume of vaccine suspension and titre is safe for use in dogs (inaccessible to parenteral vaccination). The safe use in dogs is considered demonstrated and the risk assessment for human exposure and safety is considered satisfactory. A more detailed description of the sachet is added to the product information.

It now reads: "The vaccine suspension is filled in sachets. The sachet consists of three laminated layers containing printed paper, aluminium foil and polyethylene and is embedded in a bait matrix attractive for the target species." The respective amended product information is provided.

Efficacy

To support the efficacy of the vaccine in dogs the applicant provided three laboratory studies on efficacy. Two development studies and one pivotal efficacy challenge studies were performed.

A study to analyse if the vaccine strain SPBS GASGAS could in principle protect dogs against a lethal rabies challenge was performed during the development of Rabitec. This study was submitted with the current variation application.

A dose finding study was performed to determine the minimum effective dose for Rabitec in dogs.

A new pivotal laboratory efficacy study employing a virulent challenge in dogs for determination of duration of immunity was performed. Furthermore, some efficacy data from field trials outside the EU are provided.

The main purpose of the field studies was the selection of an attractive bait material for dogs and the demonstration of immunogenicity of the vaccine strain SPBN GASGAS in local dogs in the field.

The first developmental study was performed during the development of Rabitec, when suitable constructs for the future product were tested for efficacy. It was added to the variation package as it contains additional data in dogs for the vaccine strain SPBN GASGAS, which was finally chosen as the active ingredient for Rabitec. Furthermore, serology in the study animals was performed making a comparison of serology data between VNT and the BioPro ELISA, the latter was also used in the current studies.

Irrespective of dose, formulation or route of administration, all vaccinated animals survived the challenge,

while all control animals succumbed to rabies within two weeks after infection. Results show that all vaccinated animals were protected from virulent challenge even though only 7/8 animals were positive in the RFFIT, while all animals tested positive in the BioPro ELISA before challenge.

The use of the blocking ELISA for monitoring of seroconversion rates of free-roaming dogs after oral vaccination with Rabitec is considered as a useful tool, data suggest it might be a reliable surrogate for protection.

The objective of the second study was to determine the minimum effective dose of the oral live rabies vaccine (Rabitec) in dogs based on seroconversion after direct oral application. Additionally, the safety of the vaccine was assessed by evaluation of the general health of the animals throughout the study.

Healthy dogs (laboratory Beagles) of 3 months of age were immunised by direct oral administration of SPBN GASGAS. Dogs were free from antibodies against rabies before start of the study.

All animals remained in good health during the entire observation period.

From the ELISA results, the applicant concluded that the minimum effective dose for SPBN GASGAS lies between $10^{7.3}$ FFU/ml and $10^{7.6}$ FFU/ml. The minimum effective dose was set at $10^{8.1}$ FFU/dose ($10^{7.6}$ FFU/ml) at the time the study was conducted and the pivotal challenge efficacy study provided in this variation application package was finally carried out with a titre of $10^{7.5}$ FFU/ml.

The pivotal efficacy study was performed in laboratory dogs negative for rabies antibodies at the start of the study. The design and results of the efficacy study comply with the requirements of Ph. Eur. 0746 as defined for foxes and raccoon dogs and the study is therefore considered valid.

The challenge model and used challenge strain are considered valid, as all control animals succumbed to rabies within a few days after challenge.

It is concluded that a duration of protective immunity has been demonstrated for 26 weeks based on the absence of clinical signs of rabies and of rabies virus absence in brain samples in 24 of 25 animals (96%) vaccinated with a dose of $10^{7.5}$ FFU/ml of the strain SPBN GASGAS used in the product Rabitec.

Even though no field trials are legally required, the applicant still provides information on field trials performed in different regions of the world, which provide information on the selection of the bait composition and on the immunogenicity of the vaccine strain SPBN GASGAS in local dogs in the field.

In some of the studies dogs were overall slightly more interested in the intestine baits, however the egg baits were also well accepted and were better suited for delivery (release) of the vaccine in the oral cavity.

In summary, in different studies around the world the egg-flavoured bait was well accepted by the local dog population irrespective of size, sex, age and level of restriction or ownership (owned, ownerless, community-owned). Besides good acceptance in the target species it was also most efficient in releasing the vaccine suspension into the oral cavity. Soft sachets were also better accepted by dogs than the harder PVC blisters. Therefore, the applicant decided to use soft sachets containing the vaccine suspension embedded in egg-flavoured baits.

This bait/container combination was therefore used in the pivotal efficacy laboratory study in dogs, resulting in a protection rate of 96% in dogs in a laboratory setting. This confirms the suitability of the vaccine container and the egg-flavoured bait for the intended purpose.

The provided serological field studies on administration of the vaccine strain SPBN GASGAS to dogs, cover different aspects of oral rabies vaccination in dogs not accessible to parenteral vaccination.

In these studies, local dogs were orally vaccinated with SPBN GASGAS. Depending on the individual study

and their parameters e.g. how the baits were offered to the dogs, a high proportion or all of the vaccinated dogs seroconverted. This confirms the immunogenicity of the vaccine strain SPBN GASGAS also in the field and not only in dogs which were bred for use in laboratory studies.

The studies also support the proposed hand-out and retrieval strategy, as it was shown that it has a low risk for exposure to humans or non-target species.

Furthermore, in some of the studies serology was monitored in parallel by RFFIT and by the BioPro ELISA, providing comparative serology data for both methods.

In summary the applicant concludes that, the data generated in these field studies for oral rabies vaccination in dogs, confirm the immunogenicity of the SPBN GASGAS strain in the field and underscore the potential of oral rabies vaccination campaigns using Rabitec in controlling rabies in dogs not accessible for parenteral vaccination.

One of the field studies was performed in a shelter in Thailand. Animals were seronegative at start of the study and were vaccinated by bait or direct oral administration with SPBN GASGAS. In parallel, another group was vaccinated subcutaneously with an inactivated commercially available vaccine and a placebo bait group and an untreated control group were included.

The applicant concludes that the study results demonstrate that SPBN GASGAS offered orally to local dogs in Thailand elicits an immune response that is comparable to results from dogs parenterally vaccinated with an inactivated vaccine.

In this study, 14/15 dogs vaccinated by bait tested positive in the ELISA by D14. Therefore, the proposed onset of immunity of 15 days, as also shown for foxes and raccoon dogs in the original authorisation procedure, is also accepted for vaccination in dogs.

Moreover, the study showed long-lasting persistence of antibodies (detected by ELISA) above the level indicative of protective immunity (BioPro ELISA (≥ 40% inhibition) for at least 30 months post vaccination. Thirty-six months after the primary vaccination a secondary vaccination with a commercially available inactivated vaccine, resulted in a fast increase of antibody titres, which indicates a booster effect.

From the results described above it is furthermore concluded that serology results determined by ELISA are more robust than those determined by RFFIT.

Similar results were obtained during the pivotal efficacy study also provided in this variation application, where the serology results obtained in the ELISA test correlated better with the results of the virulent challenge as the results of RFFIT and are therefore evaluated as a possible surrogate of protection.

Taking these data into consideration, it is concluded that the use of the BioPro ELISA is suitable for determination of serology data in oral rabies vaccination campaigns in dogs not accessible to parenteral vaccination. Serological data generated with the ELISA in a field study, indicate persistence of rabies specific antibodies in dogs vaccinate in the field for 30 months.

In conclusion, controlled clinical trials supported by several field trials demonstrate that a minimum dose of Rabitec ($10^{7.5}$ FFU/ml in a volume of 3 ml) administered by sachets coated with a gelatine bait matrix is safe and efficient to vaccinate dogs (not accessible to parenteral vaccination) against rabies.

The proposed SPC claims that the product is efficacious for the active immunisation of dogs inaccessible for parenteral vaccination against rabies to prevent infection and mortality. Onset of protective immunity is expected from 15 days after vaccination. Duration of immunity is indicated by the applicant as at least 30 months.

The applicants' proposal for indication and an onset of immunity of 15 days is supported. However, duration of immunity by a laboratory study including a virulent challenge was demonstrated for 26 weeks. Serological

data from the field, measured by ELISA, indicating positive antibody titres for up to 30 months in dogs after uptake of baits is provided. However, in this field study no virulent challenge was performed. Therefore, a duration of immunity in dogs of 26 weeks as demonstrated by challenge is accepted. Further information on the serological data from field trials (positive ELISA serology for 30 months) is included in the product information as additional information.

2.1. Quick Response (QR) code

With this application, the applicant has submitted request for the provision of information via a Quick Response (QR) code in the labelling of the bait for dogs which will be the same as currently authorised for raccoon dogs and foxes. The information will be provided to users by means of text.

The submitted QR code is acceptable and in line with the product information.

3. Benefit-risk assessment of the proposed change

This product is authorised for the active immunisation of foxes and raccoon dogs against rabies to prevent infection and mortality.

The proposed variation is to add:
- a new a strength (infectivity titre) including a new target species (dogs);
- a new composition of the bait (for the new target species dogs) and
- a new vaccine container (sachet - for the new target species dogs).

3.1. Benefit assessment

Direct therapeutic benefit

Rabies is a notifiable, viral zoonotic disease responsible for many human deaths world-wide each year, most of these cases are due to dog-mediated rabies transmitted by free-roaming dogs as reservoir species. Furthermore, there is a risk for re-introduction of rabies to the wildlife by dog bites. In developed countries dog-mediated rabies has been largely eliminated by mass vaccination of dogs and further management measures, but globally, the dog is the most important reservoir, particularly in developing countries.

The applicant’s live attenuated rabies vaccine Rabitec is currently registered for the oral immunisation of foxes and raccoon dogs. With this application, the applicant wishes to add dogs not accessible to parenteral vaccination as target species for Rabitec. The vaccine is presented in a different strength and dose volume, resulting in a higher minimum titre.

To support this claim, new results for efficacy of Rabitec in dogs are provided and already available results for target animal safety are discussed and supported by target animal safety data from field studies.

Due to the slightly different preferences and behaviours of dogs and foxes or raccoon dogs a new composition of the bait and a new vaccine container (a sachet instead of a blister package) are also introduced.

Controlled clinical trials demonstrated that the product is efficacious in dogs (not accessible for parenteral vaccination). The following SPC claims are proposed by the applicant:

For the active immunisation of dogs inaccessible for parenteral vaccination against rabies to prevent infection

and mortality.

Onset of immunity: Protective immunity is expected from 15 days after vaccination.

Duration of immunity: 26 weeks as demonstrated by virulent challenge in dogs
Serological data (ELISA) from dogs vaccinated in the field indicate the persistence of protective rabies specific antibody titres for at least 30 months.

The proposed benefit of Rabitec is its efficacy in dogs inaccessible to parenteral vaccination investigated in the pivotal well-designed laboratory challenge study conducted to an acceptable standard.
These data are supported by data from several field studies from outside Europe.

The bait/container combination used in the pivotal efficacy study in dogs resulted in a protection rate of 96% in dogs, but it seems according to the efficacy rate is considerably less in field conditions.

The seroconversion rate obtained under field and experimental conditions is multifaceted and does not depend solely on vaccine attributes. Antibodies are the primary mechanism of protection against rabies infection, however immunity to rabies is complex, involves humoral and cell-mediated immunity and interactions between the innate and adaptive immune response.

Additional benefits

The applicant states that the approval of dogs as a target species by EMA will facilitate the approval process outside of the European Union. Adding dogs as a target species will contribute to the global plan to eliminate dog-mediated human rabies by 2030.

3.2. Risk assessment

Quality:

Information on development, manufacture and control of the new vaccine container (sachet) and bait (egg bait) has been presented in a satisfactory manner. The results of tests carried out indicate in general consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product in general should have a satisfactory and uniform performance in clinical use. Due to the slightly different preferences and behaviours of dogs and foxes or raccoon dogs a new composition of the bait and a new vaccine container (a sachet instead of a blister package) are introduced. The new vaccine container is a soft paper-based sachet instead of a PVC blister. It was demonstrated that the newly selected bait material is attractive to dogs and does not have a negative impact on the uptake of the vaccine.

Safety:

The safety of the vaccine strain SPBN GASGAS is considered demonstrated for dogs.

In one of the safety studies, the original authorisation procedure for Rabitec, safety in dogs as a non-target species was monitored. The study fulfils the requirements for safety in the target animal, except for the number of dogs that were monitored and the titre for the 10-fold overdose.

As the titre used for vaccination in dogs is higher than that for foxes and raccoon dogs, the tested overdose in dogs is not the tenfold overdose. However, taking into consideration the provided data and keeping in mind the 3R principles to avoid unnecessary studies in animals, the CVMP agreed to the applicants' request

to omit further safety studies in a scientific advice from 2020.

The applicant now proposes a slightly higher maximum release titre, to avoid an increased risk of non-conform batch testing results and subsequently non-availability of the product for dogs to the market. This should be avoided considering the WHOs strategy: "Zero by 30: the global strategic plan to end human deaths from dog-mediated rabies by 2030" in which every available vaccine batch against rabies is considered valuable.

While this newly proposed titre slightly exceeds the titre of the batch which was used in a dog safety study. the same arguments as already discussed during the scientific advice procedure in 2020 based on the 3R principles and the overall safety data available, likewise apply for this slightly further elevated titre.
The safety profile of the vaccine strain SPBN GASGAS was assessed as very good, and it is not expected that the proposed increase of the maximum release titre will change the safety profile of Rabitec perceptibly.

Some additional safety data is provided from field studies, which were performed in several countries, with the main purpose to select an appropriate bait material attractive to dogs and to demonstrate the immunogenicity of the vaccine strain in dogs in the field. No severe adverse events were observed during these studies.

Risks for the target animal:

Administration of Rabitec to the new target species dogs not accessible to parenteral vaccination at the new dosage in accordance with SPC recommendations is generally well tolerated. The hard blister used for foxes and raccoon dogs may cause injuries in the pharynx and the buccal cavity of dogs as their eating behaviour differs from those of foxes and raccoon dogs. The soft sachet reduces this risk and also the risk of gastro-intestinal obstructions if the container is swallowed.

Risks for the user

The risk assessment for human exposure and safety is considered satisfactory. The risk for human exposure can be considered low. The risk for the occurrence of serious adverse events in humans can be considered even lower.

In summary, in the CVMP's view from all information provided on the safety profile of the vaccine strain SPBN GASGAS, it is not to be expected, that the now proposed, slightly higher maximum release titre of 9.5 $\log_{10}$ FFU/dose, will result in an increased risk for the target animal, non-target animal, accidentally exposed humans or the environment compared to the titre of 9.1 $\log_{10}$ FFU/dose for which safety in dogs was demonstrated in the non-target-species study in dogs, during the initial marketing authorisation for foxes and raccoon dogs. The safety profile of the vaccine strain SPBN GASGAS is considered very good and it is not expected that the proposed increase of the maximum release titre will change the safety profile of Rabitec perceptibly.

Therefore, the CVMP concludes that the proposed, slightly higher maximum release titre of 9.0 $\log_{10}$ FFU/ml (9.5 $\log_{10}$ FFU/dose) can be accepted, even if it slightly exceeds the maximum titre for which safety was demonstrated in a study in dogs.

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 environment and to provide advice on how to prevent or reduce these risks.

3.4. Evaluation of the benefit-risk balance

The product has been shown to be efficacious for dogs not accessible to parenteral vaccination to prevent infection and mortality by virulent challenge.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product for dogs which includes a new vaccine container (sachet instead of PVC blister) and a new bait material (egg-flavoured bait) should have a satisfactory and uniform performance in clinical use.

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

4. Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) considers that the application for a variation to the terms of the marketing authorisation for Rabitec can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows:

- I.II.1.c - Changes to strength, pharmaceutical form and route of administration - Change or addition of a new strength/potency

Changes are required in the following Annexes to the Community marketing authorisation: I, IIIA and IIIB. Please refer to the separate product information showing the tracked changes.

As a consequence of this variation, a combined product information with separate SPC, labels and package leaflet for the target species foxes and raccoon and dogs is provided.

Recommendation

It is recommended that the applicant provides the following information after the approval of the variation: Further confirmatory information needs to be provided on the details and validation of sterilisation of the foil to be used for sachet production by gamma radiation. The applicant provided a confirmation letter, which indicates that data on the sterilisation of the foil used will be provided as soon as they are available but before the end of 2024 at the latest.

Additionally, during variation EMEA/V/C/004387/VRA/0012 for Rabitec, which ran in parallel and was finalised in the meant time, a recommendation concerning submission of the outstanding stability data on the final product was included. As these data are also relevant for the current variation EMEA/V/C/004387/VRA/0011, it is referred to this recommendation. A further recommendation is not considered necessary, as the same subject is covered for both variations.