EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 January 2020
EMA/56879/2020
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for a type II variation for Rabitec (EMEA/V/C/004387/II/0002)

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

Rapporteur: Esther Werner

Co-rapporteur: Katariina Kivilahti-Mantyla

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

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, IDT Biologika GmbH (the applicant), submitted to the European Medicines Agency (the Agency) on 23 July 2019 an application for a type II variation for Rabitec.

1.2. Scope of the variation

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

To extent the duration of immunity of the product from 6 to 12 months.

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 and Part 4

1.4. Scientific advice

The applicant received scientific advice from the CVMP on 13 August 2015 (EMA/CVMP/SAWP/553740/2015). The scientific advice pertained to non-clinical and clinical aspects of the dossier.

The applicant followed the scientific advice given by CVMP.

1.5. MUMS/limited market status

The applicant requested MUMS classification for this product by the CVMP, and the Committee confirmed at their 8-10 April 2014 meeting that, where appropriate, the data requirements in the appropriate CVMP guidelines on minor use minor species (MUMS) data requirements would be applied when assessing the application. MUMS status was granted for the following reasons:

As the target species foxes and raccoon dogs are minor species, the product is indicated for MUMS/limited market.

2. Scientific Overview

With this variation the applicant applies for an extension of the duration of immunity for Rabitec from 6 months to 12 months. Quality and safety of the product remain unchanged.

2.1. Extension of Duration of immunity from 6 to 12 months

To demonstrate this, the applicant provided a new efficacy study in foxes employing a challenge 53 weeks after vaccination, the respective batch protocol, a justification for the omission of a study in raccoon dogs, including several publications on comparability of the immune response in foxes and raccoon dogs and considerations on animal welfare in experimental procedure.

An additional laboratory efficacy study was performed at two different sites in foxes. The challenge strain is classified as pathogen of risk level 3; therefore, the housing also has to correspond to the BSL-3 standard. There is only a limited number of these experimental laboratories available, therefore it is acceptable that the study was performed at two different sites. The challenge strain used in this study (CVS Fox Krefeld FLI ID 148) was also used in the studies submitted during the authorisation procedure of the product.

Animals were randomly allocated to two treatment groups.
5 days before treatment blood samples were taken to confirm the seronegative status.

Group 1 (31 animals) received a vaccine bait of minimum potency
Group 2 (15 animals) received a placebo bait

53 weeks after bait uptake animals were challenged intramuscularly.

The requirement from respective Monograph 0746 of at least 25 vaccinated animals and at least 10 control animals is fulfilled. More than 90% of the control animals succumbed to rabies, therefore the study is considered valid.

All data provided show that: duration of immunity of 53 weeks in foxes was demonstrated after uptake of one bait of Rabitec containing the minimum titre as authorised.

The applicant provides a detailed justification for his decision to perform the additional duration of immunity studies in foxes only and not in raccoon dogs.

Rabitec is a MUMS product, therefore DOI studies are allowed to be performed after marketing authorisation. The applicant reasons that in light of the 3R principles, taking also into account guideline 2010/63/EU, it is not desirable to use more animals than necessary, especially in this kind of severely harmful trial. Furthermore, the trial has to be performed under BSL-3 conditions; capacities for laboratories fulfilling these requirements are limited. Additionally, raccoon dogs are considered an even more minor species than foxes. Therefore, the applicant considered omission of an additional study in raccoon dogs as applicable.

The Rapporteurs agree with this decision.

The serology data generated in the new DOI study (12 months) in foxes, was compared to the data obtained from the original DOI study from the marketing authorisation procedure. It can be concluded that the data are comparable and a similar dynamic of the antibody kinetic in raccoon dogs can be assumed also for the months 7 to 12 after vaccination.

Furthermore, several publications were provided, discussing the comparability of antibody responses to rabies between foxes and raccoon dogs, providing information on the stipulation of cut-off values of both tests used for serology and considerations for animal welfare in experimental studies.

The extrapolation of serology data for raccoon dogs from the data generated in foxes is accepted. The DOI of 12 months for Rabitec is considered demonstrated in foxes and raccoon dogs.

The applicant provided detailed tables describing the changed dossier wording.
The only change in the product information is the extension of the DOI from 6 to 12 months in Section 4.2 of the SPC and Section 4 of the package leaflet.

It was concluded that duration of immunity of 12 months has been demonstrated by a challenge at 12 months post vaccination in foxes and by satisfactory justification in raccoon dogs.

3. Benefit-risk assessment of the proposed change

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

The authorised duration of immunity was at least 6 months.

This variation is to extend the duration of immunity of the product from 6 to 12 months.

The product has been classified as MUMS and therefore reduced data requirements apply, which has been considered in the assessment.

3.1. Benefit assessment

Direct therapeutic benefit

The direct benefits of the product remain unaffected by this variation. However, currently the vaccination campaigns are usually performed twice a year, usually in spring and autumn. As the occurrence of rabies in Europe is regressing, a more cost-effective approach could be pursued, and an annual campaign may be established. Therefore, the demonstration of the DOI of 12 months for Rabitec is favourable.

3.2. Risk assessment

The overall risk assessment for the product remains unchanged in comparison to the assessment at the time of the initial marketing authorisation procedure.

Quality:

Quality remains unaffected by this variation.

Safety:

No change for the safety profile of the product as assessed during the initial marketing authorisation procedure results from the variation introduced to extend the duration of immunity from 6 to 12 months; neither for the target animal, the user or the environment, as neither the composition nor the administration route of the product was amended. No additional or more intense adverse events were monitored in the additional satisfactory efficacy study in foxes.

Risk management or mitigation measures

The variation does not affect the risk management or mitigation measures as they were assessed and accepted in the initial marketing authorisation procedure.

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

Efficacy

The DOI of 12 months for Rabitec was demonstrated in foxes and the data were considered to be transferable to raccoon dogs without further study.

3.3. 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 and target animal safety, as the variation only affects efficacy.

The extension of the DOI from 6 to 12 months does not alter the benefit-risk balance, as assessed during the initial marketing authorisation procedure.

The overall benefit-risk balance is considered to remain unchanged.

4. Conclusion

Based on the original and complementary data presented on efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Rabitec can be approved. The CVMP considers that the benefit-risk balance remains positive and, therefore, the variation is considered approvable.

Duration of immunity of 12 months was demonstrated in foxes and extrapolated employing serology data for raccoon dogs.

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

I and IV

As a consequence of this variation, section 4.2 of the SPC is updated. The corresponding section of the Package Leaflet is updated accordingly.