Institute for State Control of Veterinary Biologicals and Medicines
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(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

RABADROP, oral suspension
(CZ, BG, DE, EE, EL, FI, HR, HU, LT, LV, PL, RO, SI, SK)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	CZ/V/0149/001/DC
Name, strength and pharmaceutical form	RABADROP, oral suspension (CZ, BG, DE, EE, EL, FI, HR, HU, LT, LV, PL,RO, SI, SK)
Applicant	Bioveta, a.s. Komenského 212/12 683 23 Ivanovice na Hané Czech Republic
Active substance(s)	Rabies virus SAD Clone attenuated
ATC Vet code	QI07BD
Target species	Red fox, raccoon dog
Indication for use	For active immunisation of wild red foxes and raccoon dogs to prevent infection by rabies virus.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	DECENTRALISED PROCEDURE application in accordance with Article 32(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	05/06/2019
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	BG, DE, EE, EL, FI, HR, HU, LT, LV, PL,RO, SI, SK

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species. Vaccine baits are not intended for vaccination of domestic animals. Suitable warnings and precautions for persons administering the vaccine to animals are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The vaccine contains the active substance:

Rabies virus SAD Clone attenuated $1.8 \times 10^{6,0}$ $TCID_{50}$* – $1.8 \times 10^{8,5}$ $TCID_{50}$*

* 50% Tissue culture infectious dose

List of excipients:

Stabilizing medium (collagen, sodium chloride, trometamol, potassium glutamate, edetic acid, water for injection)

Bait material no. 1:

Beef tallow, hard paraffin, paraffin oil, fish meal, biomarker - tetracycline hydrochloride

Bait material no. 2:

Palm oil, fish meal, hard paraffin, bergafat, biomarker - tetracycline hydrochloride

Bait material no. 3:

Beef tallow, palm oil, fish meal, hard paraffin, bergafat, biomarker - tetracycline hydrochloride

The biomarker may not be part of the bait if required by specific tender conditions. Non-use of the biomarker has no negative impact on the acceptability of baits.

One dose of vaccine is filled into aluminium-PVC plastic blisters, covered with bait.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site. A corresponding manufacturing licence and GMP certificates are provided.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is Rabies virus SAD Clone attenuated, which is established active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with this specification have been provided.

Starting materials of non-biological origin used in production comply with indicate pharmacopoeia monographs or in-house specifications.

Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur monographs and European guidelines, any deviation was adequately justified.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline and satisfactorily tested according to current European requirements.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies:

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control tests during production

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

E. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. Relevant validations are provided.

The tests include in particular:
- appearance
- determination of tetracycline hydrochloride (biomarker) content
- extractable volume
- identity test of vaccination antigen
- verification of pathogenicity of the virus after intracerebral administration to adult mice
- extraneous agents
- mycoplasma
- virus titre
- sterility

F. Batch to batch consistency

The demonstration of the batch to batch consistency is based on the results of 3 batches produced according to the method described in the dossier.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.
Based on the results of the tests of the vaccine the stability of bulk of the vaccine for 3 months was demonstrated when stored under the approved conditions 2-8 °C.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (24 months) when stored under the approved conditions (-20°C and lower). Stability data have been provided also on the case when the vaccine is defrosted within its shelf life, however not later than 21st month of the shelf life, then the vaccine can be stored under the approved conditions +2°C and +8°C and used for 90 days after defrosting.

Stability of preparation under laboratory conditions was shown for 7 days at 25°C, 5 days at 30°C and 3 days at 35°C.

H. Other Information

Non applicable.

III. SAFETY ASSESSMENT

RABADROP, oral suspension is a monovalent live virus vaccine and is indicated for vaccination of wild red foxes and raccoon dogs to prevent infection by rabies virus.
The live virus component of the vaccine is presented in liquid form in a plastic blister placed in a bait of round or die shape and of a solid consistency.

Safety studies have been performed with a vaccine batch with maximum antigen content produced according the described production process.

Laboratory trials

Overarching guidance on the safety testing of veterinary vaccines is provided by Directive 2001/82, Annex I, Title II as amended by 2004/28/EC, as well as current Ph.Eur. – general chapter 5.2.6 Evaluation of safety of veterinary vaccines and immunosera and monograph 0746 Rabies vaccine (live, oral) for foxes and raccoon dogs.
For laboratory safety testing Ph.Eur 5.2.6 states that “dose” means that quantity of the product to be recommended for use and containing the maximum titre or potency likely to be contained in production batches. The monograph therefore requires that one dose of vaccine RABADROP, oral suspension should contain the maximum titre of antigen.
The safety of a single and repeated dose, overdose as well as the dissemination and the spread of vaccine virus and the verification of stability of the genetic marker were tested using the batch of vaccine/the batch of antigen containing the maximum potency/titre of rabies component. Vaccine batches for safety studies were blended according to the manufacturing processes outlined in Part 2. Release protocols for all batches used in the safety trials were provided. Both target species (foxes and raccoon dogs) were involved in safety studies. Foxes and Raccoon dogs enrolled in safety studies were older than 3 months and were sourced from wild catching. The animals had not antibodies to rabies.
In conclusion the vaccine RABADROP, oral suspension was considered safe after the administration of a single dose, repeated a single dose and also when target and non-target animals were vaccinated with overdoses of the vaccine components. The vaccine RABADROP, oral suspension complies with the requirements of European Pharmacopoeia general chapter 5.2.6 and Monograph 0746.
Special Requirements for Live Vaccines: the assessment of dissemination, the spread of vaccine virus and the stability of the Rabies SAD Clone vaccine strain has been achieved.
The vaccine strain SAD Clone hasn´t the potential for spreading animal-to-animal.
The vaccine RABADROP, oral suspension is intended for manual placement and for placement from an airplane. The persons who manipulate with this vaccine should be trained. This information is described in the Summary of Product Characteristics and Package Leaflet. The area where the oral vaccination is going on should be signed. If the product will be handled according to the instructions in the Summary of Product Characteristics and Package Leaflet, the risk for users is very low.

Field studies

According to the Committee for Medicinal Products for Veterinary Use (CVMP), RABADROP, oral suspension was considered as immunological veterinary medicinal products intended for minor use or minor species (MUMS).
The results of laboratory safety studies are representative for safety under field conditions. In accordance with the Guideline EMA/CVMP/IWP/123243/2006-Rev.3: „If laboratory studies adequately demonstrate the absence of a significant target animal safety risk, field studies are not required“.

Environmental Risk Assessment

The applicant provided a first phase of environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

The assessment concluded that there is a negligible risk to the environment associated with use of the vaccine. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

RABADROP, oral suspension is a monovalent live virus vaccine and is indicated for vaccination of wild red foxes and raccoon dogs to prevent infection by rabies virus.
The live virus component of the vaccine is presented in liquid form in a plastic blister placed in a bait of round or die shape and of a solid consistency.

The vaccine batches with minimum antigen content used in the laboratory trials were manufactured using the procedure described in the marketing authorisation documentation.

Laboratory Trials

The assessment on Part IV – Efficacy is based on the general requirements of Directive 2001/82/EC as amended, Annex I, Title II, as well as current Ph.Eur. – general chapter 5.2.7 and monograph 0746 Rabies vaccine (live, oral) for foxes and raccoon dogs. Since the vaccine is designated for the use in foxes and raccoon dogs, the “Guideline on data requirements for immunological veterinary medicinal product intended for minor use or minor species (MUMS/limited market)” (EMA/CVMP/IWP/123243/2006-Rev.3) can be taken into account.

Laboratory studies have been performed for verification of efficacy: the duration of immunity was established for foxes and raccoon dogs by challenge. The efficacy of the vaccine RABADROP, oral suspension has been fully established according to the requirements of the Ph. Eur. and Directive 2001/82.
The batch with a minimum virus titre was used for all efficacy studies.
Study of the determination of the minimum dose of the vaccine strain SAD Clone has confirmed very good immunogenicity of the vaccine strain.
The efficacy of the vaccine strain was confirmed as well as the efficacy of the biomarker in the baits.

Field Trials

According to the Committee for Medicinal Products for Veterinary Use (CVMP), RABADROP, oral suspension was considered as immunological veterinary medicinal products intended for minor use or minor species (MUMS).
In accordance with the Guideline (EMA/CVMP/IWP/123243/2006-Rev.3):
”Field studies are not required if laboratory efficacy studies adequately establish and validate the efficacy and it is justified that they are representative of efficacy under field conditions“.
In conclusion the results of laboratory efficacy studies are representative of efficacy under field conditions and a laboratory challenge model was proved to be relevant to EU field situation and reproducing relevant clinical signs.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

None