MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD

agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

BLUEVAC- 4

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0268/001/MR
Name, strength and pharmaceutical form	BLUEVAC- 4 ≥ $10^{6.8}$ $CCID_{50}$* Suspension for injection
Applicant	CZ VETERINARIA S.A
Active substance(s)	Bluetongue virus inactivated, serotype 4, strain BTV-4/SPA-1/2004
ATC Vet code	ATCvet codes: sheep QI04AA02; cattle: QI02AA08
Target species	Sheep and cattle
Indication for use	**Sheep** Active immunisation of sheep to reduce the viraemia* and clinical signs caused by the serotype 4 of the Bluetongue virus. *(Cycling value (Ct) ≥ 36 by a validated RT-PCR method, indicating no presence of viral genome) Onset of immunity: 21 days after completion of the primary vaccination scheme. Duration of immunity: 1 year after completion of the primary vaccination scheme. **Cattle** Active immunisation of cattle to reduce the viraemia* caused by the serotype 4 of the Bluetongue virus. *(Cycling value (Ct) ≥ 36 by a validated RT-PCR method, indicating no presence of viral genome) Onset of immunity: Has not been established by challenge Duration of immunity: 6 months after completion of the primary vaccination scheme

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	28/04/2016
Date product first authorised in the Reference Member State (MRP only)	31/10/2006
Concerned Member States for original procedure	EL, DE

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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; the slight reactions observed are indicated in the SPC.
The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions 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. Composition

BLUEVAC-4 is an inactivated vaccine against bluetongue, that contains bluetongue virus, strain BTV-4/SPA-1/2004 of serotype 4, in quantity of $10^{6.8}$ $CCID_{50}$ per dose of 2 ml, and aluminium hydroxide, saponin, thiomersal and phosphate-buffered saline as excipients.

The container/closure system are 50, 100 and 250 ml high density polyethylene bottles, with perforatable butyl rubber stopper and aluminium seal. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the adjuvant, vaccine strain and formulation are justified.

The inactivation process and the detection limit of the control of inactivation are correctly validated.

The product is a suspension for injection 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 from a licensed manufacturing site.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is the bluetongue virus, strain BTV-4/SPA-1/2004 of serotype 4. The active substance is manufactured in accordance with the principles of good manufacturing practice.

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 Guidelines.

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

D. 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.

E. Control tests during production

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

F. 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. The tests include in particular tests of general characteristics, identification of active substance, antigen quantification and batch potency, identification and assay of adjuvants and excipient components, sterility/purity and inactivation.

The demonstration of the batch to batch consistency is based on the results of 3 consecutive production batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

G. Stability

Stability data on the active substance have been provided, demonstrating the stability when stored under the approved conditions.

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 when stored under the approved conditions.

III. SAFETY ASSESSMENT

The laboratory tests have been carried out with batches of BLUEVAC vaccines, including BLUEVAC-4, in order to support the safety of this one. All these vaccines have the same composition in terms of excipients.

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal (sheep and cattle) is demonstrated in a total of 16 and 11 laboratory studies respectively, with BLUEVAC vaccines which have the same manufacture process of the antigens in all the cases. Thus, data of these studies can be assumed for BLUEVAC-4.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

The vaccine is safe for the target species from the minimum recommended age, using the recommended scheme of vaccination of 2 doses of 2 ml, by subcutaneous route.
The vaccine does not induce adverse or systemic reactions for 14 days after the administration; the increase of body temperature is within the normal limits for each species. The only observed reaction is a local nodule in a few cases, that does not affect to general health status of the animals, and the progress throughout the study is favourable. These reactions are set in the SPC accordingly with the obtained results.

Effects on reproductive performance were examined: the vaccine is safe in pregnant females and does not affect to the reproductive performance, nor the spermatic quality of breeder males or fertility. The SPC reflects these conclusions.

The immune response obtained after the administration of the BLUEVAC vaccines to sheep and cattle was studied in terms of serotype-specific neutralising antibodies and anti-VP7 antibodies. The administration of the vaccine did not induce adverse effects on the immune function of the vaccinated animals.

The vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

The adjuvant and excipients used are aluminium hydroxide, saponin, thiomersal and phosphate-buffered saline, and with reference to MRL regulation, no withdrawal period is proposed.

No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

Field studies

Three field studies carried out on sheep and cattle with BLUEVAC vaccines, two of themon sheep and the last one in cattle. The results support the safety in the both species in the field conditions.

Ecotoxicity

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

The virus is not contagious for the human. The risks for the user are limited to an accidental self-injection, and the information about it is set in the SPC and label.

The consequences associated to the administration for the environment are nil.

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)

Clinical Studies

Laboratory Trials

The applicant has conducted dose determination and confirmation studies in sheep: 2 months sheep were vaccinated with two doses 3 weeks apart (one control unvaccinated group) of each different dose level, by subcutaneous route. All of the sheep were challenged 21 days after the second dose with an infective dose of a virulent BTV-4strain. No viraemia was detected in any of the vaccinated animals with $10^{6.5}$ $DICC_{50}$/ml. The study support the indications stated for the vaccine with the antigenic concentration stated on the SPC, of reduction of viraemia and clinical signs. The onset of the immunity has been also sustained in 21 days after the second dose.

One efficacy was carried out in cattle: sero-negative 3-4 months Friesian calves were vaccinated with two doses 4 weeks apart with BLUEVAC-4 (one control unvaccinated group) by subcutaneous route. The animals were challenged after the second dose with an infective dose of a virulent BTV-4 strain.
The results of the studies in cattle support the indication stated for the vaccine (prevention of the viraemia). Nevertheless, the Applicant commits to support the onset of immunity of BLUEVAC-4 at 21 days by challenge in cattle.

Regarding with the duration of the immunity, one study was carried out in sheep. The administration of two doses of the vaccine protects against Bluetongue virus serotype 4 367 days after the second dose of the vaccine.
With respect cattle, in terms of reduction of the viraemia, a duration of immunity of 6 months has been sustained and this is stated on the SPC (section 4.2).

With respect the interference with maternally derived antibodies, two studies were carried out in sheep. The results established that the interference with maternal antibodies at 2.5 months of age in sheep is very low. Accordingly with this, information about that is set in the section 4.4. of the SPC.

Field Trials

The applicant has conducted one field study with BLUEVAC vaccine. Twelve sheep were vaccinated with two doses of BLUEVAC-1 or BLUEVAC 1+4 by subcutaneous route in the neck. After that, the animals were challenged with serotype 1 of the Bluetongue virus. The study only supports the efficacy of the serotype 1 in sheep.

Accordingly with this, and taking into account the difficulties to perform the field studies for Bluetongue, the efficacy of BLUEVAC-4 has been fully supported with the previous laboratory studies. No field trials are necessary for it.

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.

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MODULE 4

POST-AUTHORISATION ASSESSMENTS

None