MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
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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

[DRAFT] PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

SYVAZUL 1
Suspension for injection for sheep and cattle

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0274/001/MR
Name, strength and pharmaceutical form	SYVAZUL 1 Suspension for injection for sheep and cattle
Applicant	LABORATORIOS SYVA, S.A.U. Av. Párroco Pablo Diez, 49-57, 24010 LEÓN, ESPAÑA
Active substance(s)	Inactivated bluetongue virus (BTV), serotype 1, ALG2006/01 E1 strain
ATC Vet code	Pharmacotherapeutic group: Inactivated bluetongue virus vaccines for sheep. ATCvet code: QI04AA02. Pharmacotherapeutic group: Inactivated bluetongue virus vaccines for cattle. ATCvet code: QI02AA08.
Target species	Sheep and cattle.
Indication for use	<u>Sheep:</u> For active immunisation of sheep to prevent viraemia* and reduce clinical signs caused by bluetongue virus serotype 1. * Cycling value (Ct) ≥ 36 by a validated method, indicating no presence of viral genome Onset of immunity: 39 days after vaccination with a single dose or 21 days after the second dose when a two dose regimen is used Duration of the immunity: one year after completion of the primary vaccination scheme <u>Cattle:</u> For active immunisation of cattle to prevent viraemia* caused by bluetongue virus serotype 1. * Cycling value (Ct) ≥ 36 by a validated method, indicating no presence of viral genome Onset of immunity: 21 days after completion of the primary vaccination scheme. Duration of the immunity: one year after completion of the primary vaccination scheme. After revaccination duration of immunity of one year is based on serological data.

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MODULE 2

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

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Article 12(3) (Directive 2001/82/EC as amended by Directive 2004/28/EC)
Date of completion of the original mutual recognition procedure	27/07/2016
Date product first authorised in the Reference Member State (MRP only)	26/05/2009
Concerned Member States for original procedure	AT, DE, FR, IT, PT

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; 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.

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II. QUALITY ASPECTS

A. Composition

SYVAZUL-1 is a suspension for injection with the following composition: inactivated Bluetongue virus (BTV) serotype 1 as active substance, aluminium hydroxide and saponin as adjuvants, thiomersal as preservative agent and silicone antifoam and PBS as excipients.

The container/closure systems are 100 or 250 ml polypropilene flask, a bromobutyl rubber and an aluminium cap, with an internal label and a cardbox with the package leaflet.
The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the adjuvant, vaccine strain, the formulation, the inactivating agent and the presence of preservative are justified.

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

The indications of the vaccine is for active immunisation of sheep and cattle to prevent viremia (and reduce clinical signs and lesions only in sheep) produced by serotype 1 of BTV and its development is adequately described in accordance with the relevant European guidelines

B. Method of Preparation of the Product

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

C. Control of Starting Materials

The active substance is the ALG2006/01 strain of BTV serotype 1, original from Algeria and isolated at Pirbrigth Institute for Animal Health (UK) from a spleen of an infected sheep. 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 Ph. Eur. and 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.

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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 secondary packaging, appearance, virus identification and potency sterility, content in saponin, aluminium and thiomersal, pH and volume.

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. Other supportive data provided confirm the consistency of the production process.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance 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.

The in-use shelf-life of 10 hours of the vaccine after opening is supported by the data provided.

III. SAFETY ASSESSMENT

Laboratory studies have been performed using pilot batches of SYVAZUL-1 and SYVAZUL 1+8 vaccines (similar vaccine that also includes serotype 8 antigen). It can consider as correct the use of the bivalent vaccine in order to demonstrate the safety of a monovalent one (as indicated in EMA/CVMP/IWP/594618/2010 "Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal product").

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Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal is demonstrated in studies that have been carried out in the both target species, using the recommended vaccination scheme in the most sensitive categories of sheep and cattle:

- Sheep: single dose (2 ml) to naïve animals or two doses (2 ml) separated 3 weeks to young animals (> 3 months of age) born to immune sheep. Annual revaccination (2 ml).
- Cattle: two doses (4 ml) separated 3 weeks, to animals > 2 months of age in naïve animals or > 3 months in animals born to immune cattle. Annual revaccination (4 ml).

The studies were designed in compliance with monograph 62 of Eur. Phar. and Directive 2001/82/EEC (as amended), taking into account that the overdose studies is only required for live vaccines.

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

In these laboratory trials the safety of the vaccine SYVAZUL-1 has been demonstrated. Based on this information (and the safety information obtained from the use of the vaccine in the field), the SPC includes some safety recommendation for the correct use of the vaccine. After vaccination, manifestation of local reactions at the injection site is very common. From 1 to 6 days after the administration, the reaction observed is an erythema associated with mild to moderate oedema. After 6 days, the reaction evolves in a painless nodule that may reach up to 3.8 cm diameter in sheep and 7 cm diameter in cattle and that diminishes progressively. Most local reactions disappear or become residual (≤ 1cm) before 70 days in sheep and 30 days in cattle. In rare occasions an abscess may appear.
A transient increase in rectal temperature, not exceeding 2 °C, during the 48 hours following vaccination, is very common.

Effects on reproductive performance were examined: it has been performed studies on pregnant and lactating females, justifying the safety on it. The safety and the efficacy of the vaccine have not been established in breeding males. In this category of animals the vaccine should be used only according to the benefit/risk assessment by the responsible veterinarian and/or national Competent Authorities on the current vaccination policies against Bluetongue Virus (BTV).

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny therefore a specific study was not carried out.

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

The adjuvant and excipients used are insert status with reference to MRL regulation. Based on this information, 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.

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Field studies

Although the requirement of the performance of field trials is necessary to support the laboratory results, SYVAZUL vaccines were granted temporary authorisations under exceptional circumstances, and thus, data derived from this use in the vaccination campaigns is valid to provide information regarding the safety and the efficacy in the field conditions.

The extensive use of the vaccines provides data from ~~32.5 and 5.5 million~~ a great number of doses of SYVAZUL 1 and SYVAZUL 1+8 sold respectively. The use on a large number of animals of different ages, with different environmental conditions or the concurrent use with other products, provides additional data about the safety.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed. The proposed recommendation has been included on the SPC.

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IV. CLINICAL ASSESSMENT (EFFICACY)

IV.B Clinical Studies

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements, which are performed on the both target species, by the recommended routes according the proposed schemes of administration (one or two doses in sheep, and two doses in cattle) and with substandard and standard doses of the active ingredient for most of the cases.

Efficacy of vaccination was demonstrated in controlled laboratory challenge studies by subcutaneous route in sheep and by intravenous route in cattle with strain BTV-1/ALG 2006 of serotype 1. At challenge, 21 (or 39) days after vaccination (depending on the number of doses), 100% of unvaccinated control animals were confirmed as infected.
A total of 254 sheep and 84 cattle were vaccinated with SYVAZUL-1 or SYVAZUL 1+8 vaccines.
100% vaccinated animals were demonstrated negative for viraemia compared to 100% unvaccinated control animals (both sheep and cattle).
The degree of clinical signs and lesions in sheep was significantly decreased among vaccinated animals compared to control animals.
The onset of immunity has been established in sheep at 39 days after a single dose and after 21 days after two doses, and in cattle, after 21 days of the second dose.
The duration of immunity has been established at 1 year of the primary course of the vaccination on the both species, justifying the full programme of vaccination and the revaccination after 1 year.
The interference with maternally derived antibodies has been assessed and according the results, there is no interference that could impact on the efficacy of the vaccine in terms of prevention of viraemia and reduction of clinical signs and lesions (in sheep), after the vaccination at the minimum recommended age.
In case of laboratory studies with SYVAZUL 1+8, the bivalent vaccine has the same composition that the monovalent one and it has been manufactured in the same way, and the use of it is acceptable in order to justify the efficacy profile in case of BTV-1 antigen, accordingly with the applicable legislation.

Mis en forme : Non Surlignage

The efficacy of the vaccine, in terms of the recommended use, can be considered as supported.

Field Trials

With respect to the field trials, the Applicant provides data of the use of SYVAZUL vaccines (including SYVAZUL 1) in several EU countries after their authorisation under exceptional circumstances, and all the conclusions are consistent with these data.

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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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