Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Syvazul BTV 3 Suspension for Injection for Sheep and Cattle

Date Created: September 2025

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Syvazul BTV 3 Suspension for Injection for Sheep and Cattle, Suspension for injection
Applicant	Laboratorios SYVA S.A. Calle Marqués de la Ensenada, 16, 28004 MADRID, SPAIN
Active substance(s)	Bluetongue virus, serotype 3 (BTV-3), strain BTV-3/NET2023, inactivated
ATC Vetcode	QI04AA02
Target species	Cattle Sheep
Indication for use	Sheep: • For active immunisation of sheep to reduce viraemia, mortality, clinical signs and lesions caused by bluetongue virus serotype 3. • Onset of immunity: 4 weeks after completion of the primary vaccination scheme. • The duration of immunity has not been established. Cattle: • For active immunisation of cattle to reduce viraemia caused by bluetongue virus serotype 3. • Onset of immunity: 3 weeks after completion of the primary vaccination scheme. • The duration of immunity has not been established.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	National Exceptional (Provisional) Marketing Authorisation (PMA) in accordance with Article 8 of Veterinary Medicine Regulations (VMRs) 2013 (Schedule 1, Para 26) as amended.
Date of conclusion of the procedure	26/06/2025

I. SCIENTIFIC OVERVIEW

This is an application, in Great Britain (GB), for a National Exceptional (Provisional) Marketing authorisation (PMA) for Syvazul BTV 3, a suspension for injection for sheep and cattle. Laboratorios SYVA have experience of manufacturing bluetongue vaccines with the authorised product, Syvazul BTV, a multi-strain vaccine composed of one or two of three BTV serotypes (BTV-1, BTV-4 and/or BTV-8). The development of the new Syvazul BTV 3 vaccine was based on this existing multi-strain vaccine.

Syvazul BTV 3 Suspension for Injection contains inactivated bluetongue virus, serotype 3 (BTV-3), strain BTV-3/NET2023. It is indicated for the active immunisation of sheep to reduce viraemia, mortality, clinical signs and lesions caused by bluetongue virus serotype 3. In cattle it is indicated for active immunisation to reduce viraemia caused by bluetongue virus serotype 3. The onset of immunity for sheep is 4 weeks after completion of the primary vaccination scheme and in cattle it is 3 weeks after completion of the primary vaccination scheme. The duration of immunity in sheep or cattle has not been established.

The product is to be administered subcutaneously in sheep from 3 months of age with a single 2ml dose. It is to be given to cattle, via the intramuscular route, from 2 months of age in naïve animals or from 3 months of age in calves born to immune cattle. The primary vaccination course consists of two 2ml doses, 3 weeks apart. Revaccination has not been established.

The product is classified as POM-V, a veterinary medicinal product subject to prescription.

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, any reactions observed are indicated in the SPC[1]. 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[2] of the product was demonstrated according to the claims made in the

[1] SPC – Summary of Product Characteristics.
[2] Efficacy – The production of a desired or intended result.

SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains inactivated bluetongue virus, serotype 3 (BTV-3), strain BTV-3/NET2023 and the excipients aluminium hydroxide, purified saponin (Quil-A) from *Quillaja Saponaria*, thiomersal, potassium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate anhydrous, sodium chloride, silicon antifoaming agent and water for injections.

The container/closure system consists of polypropylene colourless vial containing 80 ml or 200 ml, with a type I bromobutyl rubber stopper, sealed with an aluminium closure. The particulars of the containers and controls performed are provided and conform to the regulation.

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

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

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

II.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 in a standard manufacturing process.

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

II.C. Control of Starting Materials

The active substance is inactivated bluetongue virus, serotype 3 (BTV-3), strain BTV-3/NET2023, a novel active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Starting materials of non-biological origin, that are listed in a pharmacopeia, comply with the relevant monographs and are provided with the appropriate Certificates of Analysis.

Starting materials of non-biological origin, that are not listed in a pharmacopeia, are the same as those used in the authorised Syvazul multi-strain vaccine that the product is based on.

All biological starting materials, apart from the virus strain, are the same as those used in the authorised Syvazul multi-strain vaccine and meet the requirements needed based on the legal basis of the application. The materials are appropriately screened for the absence of extraneous agents according to the relevant 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.

The proposed immediate packaging and package size are the same as those used for the authorised multi-strain vaccine. The Certificates of Analysis provided for the packaging are acceptable.

II.C.4. Substances of Biological Origin

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.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

The tests performed during production are described and acceptable for the legal basis of the application.

II.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. The tests include analyses of appearance, pH, volume, identification of the active substance, sterility and potency.

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

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

II.F. Stability

Preliminary stability data on the finished product and data from the manufacturer's authorised multi-strain vaccine have been provided in accordance with applicable regulatory guidelines, to support the shelf-life recommendations for the vaccine.

The in-use shelf-life of the broached vaccine is supported by data on the authorised multi-strain vaccine, which is acceptable due to the legal basis of the application.

G. Other Information

The shelf life of the product as packaged for sale is 2 years. The shelf life after first opening the immediate packaging is 10 hours.

The product should be stored and transported refrigerated (2 °C – 8 °C) and not frozen. The product should be protected from light and stored in the original package.

III. SAFETY ASSESSMENT

Laboratory trials

As is acceptable for the legal basis of this application, data was submitted on the safety of the similar authorised product Syvazul BTV. This comprised 6 studies in sheep and 2 studies in cattle.

The laboratory safety studies in sheep with Syvazul BTV were carried out in the most sensitive category of the target species, using the recommended route of administration. Batches of vaccine used were manufactured with the maximum number of strains (n=2) or one strain and contained either two times or eight times the fixed target antigen amount at the formulation step. The studies investigated the safety of the administration of a single dose and two repeated single doses in lambs (total of three doses 16 and 14 days apart), the safety of an overdose and a repeat single dose in lambs. An additional study conducted with mono-strain vaccine Syvazul BTV-1 was provided, evaluating safety of an overdose and repeat single dose in lambs.

The laboratory safety studies in cattle with Syvazul BTV were carried out in the most sensitive category of the target species, using the recommended route of administration. Batches of vaccine used were manufactured with the maximum number of strains (n=2) and contained either two times or eight times the fixed target antigen amount at the formulation step. The studies investigated the safety of the administration of a single dose and two repeated doses in calves. Laboratory studies were not carried out examining reproductive performance in cattle. The safety in pregnant and lactating cattle was investigated as part of field studies.

Safety data was also provided for the Syvazul BTV 3 vaccine in sheep and cattle. Two combined safety/efficacy studies carried out in 11–12-month-old sheep and in 3-4-month-old lambs were submitted alongside a single combined safety/efficacy GLP-compliant study carried out in minimum age calves.

The first study in sheep included 24 sheep where the vaccine was administered as recommended and compared to a control. The study concluded that the administration of one dose of Syvazul BTV 3 vaccine containing an antigen input of 107.2 $CCID_{50}$/ml and administered by the recommended route to 11–12-month-old sheep, is considered safe.

The second study in thirty 3-4-month-old lambs, investigated the repeated administration of two single doses. The two doses were given subcutaneously (SC), 28 days apart and a control group was included. The study concluded that the repeated administration of two doses of Syvazul BTV 3 vaccine containing an antigen input of 107.2 $CCID_{50}$/ml to animals of the youngest recommended age,

is considered safe. Adverse reactions observed in both sheep studies have been adequately reflected in the SPC.

In the cattle study, safety of the repeated administration of one dose of Syvazul BTV 3 was investigated. Thirty unvaccinated calves of approximately 9-11 weeks of age were either given the vaccine twice via the intramuscular route or a control injection, 3 weeks apart. The study concluded that the administration of a single dose and the repeated administration of two doses of SYVAZUL BTV 3 with an antigenic content of 106.9 $CCID_{50}$/ml or of 107.2 $CCID_{50}$/ml, are considered safe in calves. Appropriate adverse reactions have been recorded in the SPC.

No studies to evaluate reproductive performance were carried out with Syvazul BTV 3. However, data for the authorised multi-strain vaccine, was accepted, and the vaccine is recommended for use in pregnancy and lactation in sheep and cattle. Safety has not been established in breeding males, therefore the SPC states that a risk/benefit approach should be used.

No examination of effect on immunological functions has been conducted for the product.

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

The adjuvant and excipients used are either allowed substances, for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required, or substances considered as not falling within the scope of Regulation (EC) No. 470/2009. Based on this information, there is no withdrawal period for the product.

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

Field studies

In support of field safety, the applicant provided information on the authorised Syvazul BTV vaccine.

Safety of the Syvazul BTV vaccine in sheep was investigated in three specific field studies. These studies evaluated safety in lambs of the minimum age (3 months), in pregnant ewes and in milking ewes. Overall, the studies showed that the administration of a single dose of the Syvazul BTV vaccine, and the repeated administration of one dose of the vaccine, is considered safe in sheep of minimum age, as well as in pregnant and lactating sheep and does not affect milk yield.

Safety of the Syvazul BTV vaccine in cattle was investigated in two field studies. These studies evaluated safety in calves of the minimum age (2 months), pregnant cows and lactating cows. Overall, the studies showed that the administration of a single dose of Syvazul BTV, and the repeated administration of one dose of the vaccine, is considered safe in cattle of minimum age, as well as in pregnant and lactating cows.

Ecotoxicity

The applicant provided an environmental risk assessment (ERA) for the Syvazul BTV vaccine. As this vaccine has an identical composition to Syvazul BTV 3, in terms of adjuvants and other excipients, this was acceptable. The ERA was stopped at Phase I, and it was concluded that Syvazul BTV is expected to pose a negligible risk for the environment, when used according to the SPC. Based on this assessment for Syvazul BTV, it can be accepted that the risk to the environment of using Syvazul BTV 3, according to the SPC, is also negligible.

No warnings regarding special precautions for the protection of the environment are therefore required.

IV. CLINICAL ASSESSMENT (EFFICACY)

The application for Syvazul BTV 3, in sheep and cattle, was supported by four efficacy studies: two challenge studies in sheep, one challenge study in cattle and one serology study in cattle.

Dose confirmation studies

The amount of antigen included in the vaccine used in the clinical studies was selected according to the previous experience in development of the authorised Syvazul BTV vaccine.

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements.

Two laboratory studies were completed to demonstrate efficacy of Syvazul BTV 3 in sheep.

The first study was performed in 11–12-month-old sheep. Animals were vaccinated with a single dose of 2 ml of vaccine, according to the recommended vaccination scheme. They were then challenged with a virulent BTV-3 isolate, administered 4 weeks post vaccination, to support onset of immunity. Clinical signs and viremia were the primary efficacy parameters assessed.

The second study tested the onset of immunity following the administration of two doses of vaccine four weeks apart to lambs of 3-4 months of age. BTV-3 neutralising antibodies were assessed post-immunisation and viraemia, BTV-3 specific clinical signs and lesions caused were assessed post-challenge.

In cattle, an immunogenicity study was performed to assess serum antibody response following vaccination as well as a challenge study, to demonstrate efficacy in calves. In both studies, two doses of the vaccine were given, separated by 3 weeks.

Onset of Immunity

In the first onset of immunity study in sheep, twenty-four, 11–12-month-old sheep were given a single vaccination subcutaneously and then challenged with an appropriate BTV-3 strain, 28 days later. A placebo group was included as a control. Vaccine efficacy was evaluated by detecting viraemia after challenge and assessing BTV-3 specific clinical signs and lesions. Results showed that a reduction in clinical signs and lesions was observed in the vaccinated groups, when compared against the control group. Additionally, post challenge, significantly higher levels of viraemia were detected in the control group compared to those that were vaccinated. The study was acceptable for the legal basis of the application and a 4-week onset of immunity for the vaccine in sheep was concluded.

A second study in thirty lambs tested the onset of immunity when two doses of vaccine were administered, 28 days apart, to lambs of 3-4 months of age. A placebo group was included as a control. The sheep were challenged with an appropriate BTV-3 strain, 30 days after the second vaccination. Vaccine efficacy was assessed by evaluating viraemia levels and BTV-3 specific clinical signs and lesions, after challenge. Results showed that there was a reduction in clinical signs and lesions, as well as a significant reduction in the level of viraemia in the vaccinated group compared to the control. This study was considered supportive as the recommended administration schedule for sheep is a single 2ml dose, rather than the two doses given in this trial.

In the onset of immunity trial in cattle, Syvazul BTV 3 was given to twenty-four calves of 14-15 weeks of age. Administration followed the recommended primary vaccination schedule, consisting of two doses, administered 21 days apart. An appropriate BTV-3 challenge was completed three weeks after the second vaccination. A placebo group was included as a control. Vaccine efficacy was assessed by evaluating viraemia levels and BTV-3 specific clinical signs and lesions, after challenge. Results showed that vaccinated animals showed a significant reduction in viraemia compared to controls. In conclusion, efficacy of the vaccine in reducing viraemia was demonstrated and an onset of immunity of 3 weeks in cattle was supported.

Duration of Immunity

No information was provided regarding the duration of immunity. Therefore, the SPC appropriately states that this has not been established.

Field Trials

No field studies were performed by the applicant, which is appropriate due to the legal basis of the application.

No studies or information were provided concerning the efficacy of Syvazul BTV 3 in the presence of maternally derived antibodies. Therefore, an appropriate warning is included in the SPC.

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 benefit/risk profile of the product is favourable.

MODULE 4

POST- AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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