Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

SBVvax, Suspension for Injection

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	SBVvax, Suspension for Injection
Applicant	Boehringer Ingelheim Animal Health UK Ltd Ellesfield Avenue Bracknell Berkshire RG12 8YS
Active substance(s)	Schmallenberg virus antigen
ATC Vetcode	QI04AA
Target species	Cattle and sheep
Indication for use	Active immunisation of sheep and cattle to prevent viraemia* caused by Schmallenberg virus. * (below the level of detection by the validated qRT-PCR method at 3.2 log10 RNA copies/ml) Onset of immunity has been demonstrated 3 weeks after the primary vaccination course. The duration of immunity has not been established. This is a Provisional Marketing Authorisation. A full set of supporting efficacy data is not available for this product.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Exceptional provisional application in accordance with the Veterinary Medicines Regulations.

I. SCIENTIFIC OVERVIEW

Schmallenberg disease is a viral infection that primarily affects cattle and sheep. Only mild symptoms tend to be seen in adult animals. However the infection targets foetal tissue, damaging both the Central Nervous System (CNS) and developing joints. This leads to Congenital Arthrogryposis-Hydranencephaly Syndrome, which, as well as neonate death, often complicates parturition. SBV (Schmallenberg virus) is thought to be transmitted via midges and possibly mosquitoes.

SBVvax is an inactivated viral vaccine that will be used to prevent viraemia caused by SBV. SBVvax is indicated for subcutaneous injection in cattle and sheep. Sheep can be vaccinated with 1 ml of the product from 2.5 months of age whilst cattle similarly receive 1 ml of the vaccine from 2.5 months of age but should also receive a second injection of 1 ml 3 weeks after the first injection. Onset of immunity has been demonstrated 3 weeks after the primary vaccination course.

SBVvax has a Provisional Marketing Authorisation as a full set of efficacy data is not available for this product. This type of Marketing Authorisation is usually applied for and issued in order to address an urgent situation e.g. new disease where there is no fully authorised product in the UK to prevent the condition. Due to the nature of the use of such drugs, a full dossier meeting all requirements for the marketing of the drug is not required, provided that the safety, quality and efficacy of the product can be supported by available data, and a favourable benefit-risk profile is determined. There is a requirement for Periodic Safety Update Reports (PSURs) to be submitted for annual reassessment of this product. Moreover, results of any additional studies must be submitted to the Veterinary Medicines Directorate (VMD).

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 frequency and seriousness of any adverse reactions observed are indicated in the SPC[1]. The product is safe for the user, the consumer of foodstuffs from treated animals

[1] SPC – Summary of Product Characteristics

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 benefit/risk analysis is in favour of granting a Provisional Marketing Authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains inactivated Schmallenberg virus antigen and the adjuvants aluminium hydroxide and saponin, as well as the excipients phosphate buffer, glycine buffer and water for injection.

The container/closure system consists of 50 ml and 200 ml polypropylene bottles sealed with butyl elastomere closure and packaged in cartons of 1 x 50 ml, 10 x 50 ml and 1 x 200 ml. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the adjuvant, vaccine strain and inactivating agent 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 European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from licensed manufacturing sites. The product is manufactured by inoculating cultured baby hamster kidney (BHK) cells with the virus, then amplifying, harvesting, clarifying and inactivating the virus to produce the viral antigen. The adjuvants and excipients are added to the antigen to form the vaccine which is sterile and packaged in the vials. 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 inactivated Schmallenberg virus, a novel pathogen. 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 the relevant European monographs.

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; 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.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and 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 preliminary results of 2 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 for appearance, pH, volume and free formaldehyde, as well as potency, inactivation and sterility and purity tests. An in vitro potency test is currently under development.

G. Stability

Limited stability data on the finished product have been provided, and the product has been granted a provisional shelf life of 1 year. The vaccine should be used immediately after broaching.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the product as packaged for sale is provisionally 1 year.
- Shelf life after first opening the immediate packaging: immediately after broaching.
- Store and transport refrigerated (2°C - 8°C).
- Do not freeze.
- Protect from light.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the administration of an overdose and the repeated administration of one dose in the target animal is demonstrated in one study in lambs and one study in calves. The investigations were performed according to the

recommendations of Directive 2001/82/EC as amended and the relevant guidelines. The reactions observed are indicated on the SPC.

In the sheep study 2.5 month old lambs were randomly assigned to form two groups, a test and control group, each containing 8 lambs. The vaccine was formulated to contain a high antigen load and the lambs in the test group were inoculated with a 2 ml SC overdose of the vaccine. The lambs then received further 1 ml doses 14 and 28 days later. The lambs in the control group received physiological saline instead of the vaccine.

The lambs were monitored post-vaccination for local reactions, general reactions and body temperature changes. In addition body-weight was measured at each vaccination and on day 42 and blood samples were taken at the beginning and end of the study to be tested for SBV titres. Vaccination was not seen to affect weight gain but an increase in temperature, on average between 0.6°C and 1.4°C, was observed in vaccinates. Injection site reactions were observed following the overdose. Local reactions tended to involve redness of the skin with one animal developing pain and another developing an abscess. Following repeat vaccinations swelling was observed in all animals and redness, when present, was transient. The study demonstrated that overdose and repeat single doses were well tolerated in lambs.

A similar study was performed in cattle. Approximately three month old calves were randomly assigned to control and test groups, 8 per group. The test calves received an overdose, 2ml SC, of the vaccine. Further doses of 2 ml were administered 14 and 28 days later. The control group was inoculated with physiological saline.

The calves were monitored post-vaccination for local reactions, general reactions and body temperature changes. In addition body-weight was measured at each vaccination and on day 42. Blood samples were taken at the beginning and end of the study to be tested for SBV titres. Weight gain was unaffected by vaccination but a mild pyrexia was observed in some animals following vaccination that lasted for one day. Local reactions were observed following injection and the reactions became worse with repeat injections. Injection site reactions consisted of large swellings that quickly reduced in size and pain was not observed. This study demonstrated vaccination of calves results in large injection site reactions that resolved quickly and were tolerated.

No investigation of effect on reproductive performance was conducted. The product is not recommended for use in pregnant cattle and sheep. It is also stated on the SPC that the product should only be used in breeding males according to a benefit/risk assessment.

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 aluminium hydroxide and saponin, which are included in Annex II of council Regulation No. 2377/90. Based on this information the withdrawal period is zero days.

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

Due to the emergency nature of this vaccine there are currently no field studies for SBVvax. This is acceptable for a Provisional Marketing Authorisation.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product is an inactivated vaccine and only small amounts are likely to reach the environment; therefore the product does not present a risk to the environment. 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

SBVvax has a Provisional Marketing Authorisation and therefore a full set of efficacy data are not available for this product.

Laboratory Trials

One study has been performed in sheep and one in cattle to determine the efficacy of the vaccine. In the sheep study 31 lambs, aged approximately 2.5 months, were randomly allocated into 5 groups of 5 lambs and one group of 6 animals acting as negative controls. Each of the 5 groups of 5 animals received 1 ml of the vaccine at different titres ($log_{10}CCID_{50}$) ranging from 5.3 – 7.3. The controls remained untreated. The lambs were challenged on day 21. All lambs received a virulent SBV strain, administered by subcutaneous route. Sheep were monitored pre- and post-challenge for clinical signs and body temperature changes. Blood samples were also taken on days 0, 21 and daily from day 22-31. Necropsy was performed on day 33.

The results of this study saw no significant clinical findings or changes in body temperature after challenge in any group. Viraemia was quantified by PCR and detected in the control animals on 3 consecutive days post-challenge. None of the vaccinates were detected viraemic by PCR (i.e.below the level of detection by the validated qRT-PCR method at 3.2 log10 RNA copies/ml) at any point in the study. The results of maximum viraemia titre and number of virus positive samples were statistically significant between the vaccinated lambs and the control lambs when a Fisher Exact or Mann-Whitney Test was performed ($p<0.05$). It was concluded that vaccination with 1 ml of the vaccine, at below or above the standard release pre-inactivation titre, prevents viraemia in lambs following SBV challenge.

A similar study in cattle involved 20, approximately 3 month old, seronegative calves divided into 4 groups of 5 animals. Two vaccine batches were formulated

to contain different amounts of the SBV antigen, 6.3 $log_{10}CCID_{50}$/ml and 6.8 $log_{10}CCID_{50}$/ml pre-inactivation titre. Cattle in Group 1 received 1 ml SC of the lower dose vaccine on days 0 and 21 whilst Group 2 received the 1 ml of the higher dose at these points. Group 3 were vaccinated with 2 ml of the higher dose on day 21 only and Group 4 acted as negative control so remained untreated. All animals were challenged on day 42 of the study. Challenge was carried out with a virulent SBV strain, administered by subcutaneous route. Calves were observed pre- and post-challenge for clinical signs and body temperature changes. Blood samples were collected on days 0, 21 and daily from day 42 to day 52. Necropsy was performed on day 52 and local injection site reactions were observed at autopsy.

The results of this study included slight increase in rectal temperature in control animals post-challenge. However, mean body temperature did not change. Only one control animal presented with pyrexia and respiratory signs. Viraemia was detected by PCR in all control animals for 3 consecutive days post challenge. None of the vaccinates were viraemic at any point in the study. The number of positive PCR samples for the vaccinates compared to the controls was shown to be statistically significant using a Fisher Exact or Mann-Whitney test ($p<0.05$). Histopathology was also performed and lesions (nodular fibrosis) in the subcutis or muscle were observed at 10 of the 25 injection sites on the 15 vaccinated cattle. It was concluded that in calves aged approximately 3 months and immunised by the SBV vaccine viraemia was prevented following SBV challenge.

Field Trials

Due to the emergency nature of this vaccine there are currently no field trials for SBVvax. This is acceptable for a Provisional Marketing Authorisation.

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 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

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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