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Publicly Available Assessment Report for a
Veterinary Medicinal Product

Rhinovac IBR Marker live Lyophilisate and solvent for suspension for injection or nasal spray for cattle.

PRODUCT SUMMARY

EU Procedure number	IE/V/0653/001/DC
Name and pharmaceutical form	Rhinovac IBR Marker live Lyophilisate and solvent for suspension for injection or nasal spray for cattle
Active substance(s)	Bovine herpesvirus 1, strain bio-27 live
Applicant	Animal Health Distributors Limited Tullow Industrial Estate Bunclody Road R93W0D8, Tullow, Carlow Ireland
Legal basis of application	Application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of procedure	30/06/2021
Target species	Cattle
Indication for use	For the active immunisation of cattle to reduce the severity and duration of clinical signs and viral excretion caused by BHV-1 (infectious bovine rhinotracheitis; IBR) infections. <u>Onset of Immunity:</u> One week after intranasal vaccination of calves from 2 weeks of age without maternally derived antibodies. Two weeks after intramuscular vaccination of calves from 3 months of age. <u>Duration of immunity:</u> Ten weeks after intranasal vaccination of calves from 2 weeks of age without maternally derived antibodies. Six months after intramuscular vaccination of calves from 3 months of age.
ATC vet code	QI02AD01
Concerned Member States	UK (NI)

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains Live attenuated bovine herpesvirus Type I (BHV-I), strain Bio-27: IBR (gE negative) at $10^{5.7}$ – $10^{7.5}$ $TCID_{50}$/ dose, with the excipients Tromethamine (TRIS), Edetic acid (Chelaton II), Sucrose, Dextran 70 and Water for Injection. The solvent excipients are Sodium chloride, Potassium chloride, Disodium hydrogen phosphate dodecahydrate, Potassium dihydrogen phosphate and Water for Injection.

The container/closure system consists of colourless glass vials with a rubber stopper and an aluminium cap. The accompanying solvent is provided in colourless glass vials closed with a rubber stopper and an aluminium cap.

The choice of the vaccine strain is justified. The vaccine strain has a deleted gE gene meaning that this vaccine, in combination with diagnostic tests demonstrating antibodies against gE, will enable to distinguish vaccinated animals (with a marker vaccine) from infected animals. The formulation of the vaccine and solvent are adequately described and justified.

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.

Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is Live attenuated bovine herpesvirus Type I (BHV-I), strain Bio-27: IBR (gE negative). 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 Ph. Eur. monographs and 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. 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.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies
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 (immunologicals)
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. The tests include in particular titration of the active ingredient, viral purity and sterility.

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

F. Stability
The active substances are fully tested to ensure compliance with specifications prior to their use in manufacture of the product.

Stability data on the finished product has 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 the reconstituted vaccine is supported by the data provided.

G. Other Information
Not applicable.

III. SAFETY ASSESSMENT

Rhinovac IBR Marker live is intended for use in cattle from 2 weeks of age. There are two primary vaccination schedules depending on the age of the animal. The first primary vaccination is in calves from 2 weeks of age without maternal antibodies up to 3 months of age; one intranasal dose from 2 weeks of age. Subsequent vaccination following intranasal administration is by administration of the primary vaccination schedule by the intramuscular route. The second primary vaccination is in cattle from 3 months of age; one intramuscular dose (2 ml) per animal from 3 months of age. Revaccination with a single dose by the intramuscular route is recommended every 6 months after completion of the primary vaccination.

Laboratory Trials

Six laboratory studies were conducted, in which the safety of the administration of an overdose and the repeated administration of one dose in the target animal was demonstrated in calves from 2 weeks of age, calves aged from 3 months of age and in pregnant cattle, in accordance with the requirements of Ph. Eur. 0696. The safety of the administration of a single dose was not investigated, as in all cases a ten-fold overdose was administered to animals, which was accepted given that it was a worst case scenario for the investigation of safety. In these studies, the vaccine batch contained antigen at the maximum dose of the vaccine strain that may be included in commercial batches. The animals included were seronegative for antibodies against IBR. Safety monitoring included daily observations for 14 days for the assessment of general health and local reactions, and monitoring of rectal temperature at appropriate time points. Safety monitoring in pregnant animals continued throughout pregnancy and parturition.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines, including the specific European Pharmacopoeia monograph for Infectious bovine rhinotracheitis (0696), the general safety monograph 5.2.6 and VICH GL 44.

Overall, the vaccine was shown to be well tolerated in the target species. The local and systemic reactions observed are described in the SPC and package leaflet. The vaccine was demonstrated to be safe for use during pregnancy and lactation.

Specific studies required for live vaccines were also conducted.

The vaccine was not shown to spread from vaccinated to unvaccinated animals, however because live virus could be recovered from nasal samples from calves that were vaccinated intranasally, although spread was not detected in the in-contact group, animals vaccinated intranasally are expected to shed the vaccine virus for up to 5 days post-vaccination, and therefore the possibility of transmission of the virus from vaccinated animals cannot be excluded. This is documented in the SPC.

The dissemination study showed that the vaccine virus could not be isolated from any of the samples tested. Although dissemination into milk was not investigated in this study, the safety of use during lactation was supported under field conditions.

The potential for reversion to virulence was investigated in accordance with requirements and no indications of reversion to virulence of the vaccine virus were observed.

Regarding the potential for recombination or reassortment of the strain used in the vaccine, while the potential for recombination of the vaccine strain with a field strain does exist, the risk is low and the resulting recombinant strain which could emerge is unlikely to present a greater risk than that which would be posed by the recombination of two field strains under field conditions.

No studies on residues have been performed. All components of the vaccine are either allowed substances according to Table 1 of Regulation (EC) No. 37/2010, or are substances considered as not falling within the scope of Regulation (EC) No. 470/2009. The proposed withdrawal period 'zero days' is accepted.

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

Field Studies

The safety of vaccination was evaluated under field conditions in one field trial conducted in one EU Member State on 3 farms. The vaccine was administered according to the recommended schedule to calves from 2 weeks of age by the intranasal route followed by the intramuscular route at 3 months of age, and to calves as a single intramuscular dose at 3 months of age, and as a single intramuscular dose to pregnant cattle. All animals were observed for adverse reactions during the study and reproductive parameters were evaluated in pregnant animals. Overall, under field conditions the vaccine was shown to be well tolerated in the target species.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the main risk to the user is accidental self-injection or accidental exposure to aerosols during nasal administration. However, the components of the vaccine are not expected to present a risk to the user. It is accepted that the use of Rhinovac IBR Marker live does not pose a risk to the user, when used in accordance with recommendations. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. Rhinovac IBR Marker live is a live viral vaccine, and vaccinated animals may shed the vaccine strain by the nasal route for up to 5 days following intranasal administration. While this did not result in spread of the vaccine strain to unvaccinated animals that were in contact with vaccinated animals, the risk of spread cannot be fully excluded and therefore appropriate precautions should be taken to avoid spread if considered necessary (noting that this vaccine is a gE- IBR vaccine, i.e. a marker vaccine). Overall, the assessment concluded that Rhinovac IBR Marker live has no undesirable effects on the environment. It is accepted that the vaccine is not expected to present a risk to the environment when used in accordance with recommendations.
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

Laboratory Trials

As stated in Part III, Rhinovac IBR Marker live is intended for use in cattle from 2 weeks of age. There are two primary vaccination schedules depending on the age of the animal. The first primary vaccination is in calves from 2 weeks of age without maternal antibodies up to 3 months of age; one intranasal dose from 2 weeks of age. Subsequent vaccination following intranasal administration is by administration of the primary vaccination schedule by the intramuscular route, noting that the duration of immunity following intranasal administration is 10 weeks. The second primary vaccination is in cattle from 3 months of age; one intramuscular dose (2 ml) per animal from 3 months of age. Revaccination with a single dose by the intramuscular route is recommended every 6 months after completion of the primary vaccination.
The vaccine is intended for the active immunisation of cattle to reduce the severity and duration of clinical signs and viral excretion caused by BHV-1 (infectious bovine rhinotracheitis; IBR) infections.
The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements, including the specific European Pharmacopoeia (Ph. Eur.) monographs for Infectious bovine rhinotracheitis (0696).
Efficacy was tested in the laboratory following administration of the vaccine by the intranasal route to calves from 2 weeks of age, and following administration of vaccine by the intramuscular route to calves from 3 months of age. The vaccine batches used in the laboratory efficacy studies were at minimum potency for live IBR vaccine virus per dose.
The vaccine does not cause production of antibodies against BHV-1 virus glycoprotein E and therefore can be used as a marker vaccine. This was shown in studies by conventional ELISA (IDEXX) test which was used to demonstrate that vaccinated animals can be differentiated from naturally infected animals.

Onset of immunity:

The efficacy in the target species was demonstrated by means of challenge trials. The design of the study to evaluate onset of immunity in calves from two weeks of age and in the study to evaluate onset of immunity in calves from 3 months of age was similar; 7 seronegative calves were included in each study; 5 calves were vaccinated in accordance with recommendations and 2 calves were included as negative controls. At the claimed onset of immunity (i.e., one week after the intranasal dose, or two weeks after the intramuscular dose) in each study all animals were challenged with a virulent strain of the IBR virus. General health, clinical signs, rectal temperature, serology, and virus isolation from nasal swabs were evaluated following challenge. The differences in these parameters were compared between the vaccinated and control groups.
It was concluded that the data supported a claim for a reduction in the severity and duration of clinical signs and viral excretion caused by BHV-1 (infectious bovine rhinotracheitis; IBR) infections.
The onset of immunity is one week after intranasal vaccination of calves from 2 weeks of age without maternally derived antibodies, and is two weeks after intramuscular vaccination of calves from 3 months of age.
Laboratory studies were provided to evaluate the influence of maternally derived antibodies (MDA) on the efficacy of the vaccine in the target species. It was demonstrated that MDA have a negative impact on the efficacy of the vaccine when administered to calves from 2 weeks of age and therefore intranasal vaccination should only be conducted in 2 week old animals without MDA. An appropriate warning is included in the relevant section of the SPC. It was shown that MDAs in calves at 3 months of age did not interfere with the response to the single intramuscular dose, therefore use in calves from 3 months of age is suitable in calves with or without MDAs.

Duration of immunity

The duration of immunity against IBR of 6 months after intramuscular administration in calves from 3 months of age without maternally derived antibodies was demonstrated in one laboratory study.
Another laboratory study evaluated the duration of immunity against IBR after intranasal administration of 2 weeks old calves. This study was also conducted in order to evaluate the impact of MDAs on the response to vaccination and included groups of both MDA positive and MDA negative animals. The results supported a duration of immunity of 10 weeks after intranasal

administration in calves from 2 weeks of age without maternally derived antibodies, whereas this was not supported in calves from 2 weeks of age with maternally derived antibodies.
Based on the 6 month duration of immunity following a single intramuscular dose, the revaccination schedule comprises of a single dose, administered at 6 month intervals following intramuscular vaccination. In calves from 2 weeks of age, the duration of immunity is 10 weeks, after which time the first intramuscular dose should be administered. Thereafter, similarly, revaccination is every 6 months.

Field Trials

A field study was performed which included three farm sites. The vaccine was administered to animals of 2 weeks of age, 3 months of age, adult and pregnant cows. However, the evaluation of the efficacy of the vaccine in these farm sites was compromised due to a high level of specific antibodies at the beginning of vaccination on all the monitored farms which meant that the antibody response could not be clearly interpreted. Thus, the study was not considered informative with respect to the efficacy of vaccination under field conditions. However, the indications for use were considered to have been supported within the laboratory efficacy studies.

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.

VI. POST-AUTHORISATION ASSESSMENTS

Note: not all variations are to be listed here, only those that materially affect the content of the original Public Assessment Report.
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 HPRA website.

This section 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.

Changes:
None.